

PROPOSALS FOR A MORE EFFECTIVE ANTIBIOTIC POLICY IN BELGIUM



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ROOS LEROY, WENDY CHRISTIAENS, CHARLINE MAERTENS DE NOORDHOUT, GERMAINE HANQUET



COLOPHON

Title:	Proposals for a more effective antibiotic policy in Belgium
Authors:	Roos Leroy (KCE), Wendy Christiaens (KCE), Charline Maertens de Noordhout (KCE), Germaine Hanquet (KCE)
Authors of chapter 7:	Philippe Vandenbroeck (shiftN), Kim Becher (shiftN), Randy Mellaerts (shiftN)
Reviewers:	Marijke Eyssen (KCE), Frank Hulstaert (KCE), Christian Léonard (KCE), Dominique Roberfroid (KCE)
External experts who were interviewed by KCE and/or by shiftN and/or attended the stakeholder workshops:	Pieter Boudrez (Medaxes), Caroline Broucke (Vlaams Agentschap Zorg en Gezondheid), Franky Buyle* (Vlaamse vereniging van ziekenhuisapothekers (VZA), Belgische vereniging van ziekenhuisapothekers (BVZA), UZ Gent), Boudewijn Catry* (Sciensano), Carl Cauwenbergh (RIZIV – INAMI), Pierre Chevalier (Ex-INAMI – RIZIV, ex-Société Scientifique de Médecine Générale (SSMG)), Diederica Claeys (FAGG – AFMPS), Samuel Coenen* (BAPCOC, Domus Medica, UAntwerpen), Michiel Costers (Ex-BAPCOC, Sint-Elisabeth Ziekenhuis Zottegem), Fabiana Dal Pozzo* (AMCRA), Joke De Backer (Vlaams Agentschap Zorg en Gezondheid), Tom De Boeck (Vlaams Agentschap Zorg en Gezondheid), Kristel De Gauquier (pharma.be), Patrick De Smedt (IVDB dierenartsenbelangen), An De Sutter* (BAPCOC, UGent), Yvan Dejaegher (BFA), Jeroen Dewulf (AMCRA, UGent), Wouter Dhaeze (Vlaams Agentschap Zorg en Gezondheid), Els Duysburgh (Sciensano), Jean-Marc Feron (UCL), Frédéric Fripiat (CHU Liège), Youri Glupczynski (UCL), Herman Goossens (BAPCOC, UAntwerpen), Lies Grypdonck* (RIZIV – INAMI), Margaretha Haelterman* (FOD Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu – SPF Santé Publique, Sécurité de la Chaîne Alimentaire et Environnement), Bart Hoet* (FAGG – AFMPS), Jozef Hooyberghs (FAVV – AFSCA), Hein Imberechts (BAPCOC, Sciensano), Anne Ingenbleek* (BAPCOC), Philippe Jeannin (AZ Jan Palfijn, Gent), Marie-Laurence Lambert (INAMI – RIZIV), Koen Magerman* (BAPCOC, Jessa Ziekenhuis, Hasselt), Didier Martens (Farmaka.be), Hanna Masson* (Vlaams Agentschap Zorg en Gezondheid), Pascal Meeus (INAMI – RIZIV), Jean-Michel Michot (INAMI – RIZIV), Dries Minne (FAGG – AFMPS), Willy Peetermans (UZ Leuven), Davy Persoons (pharma.be), Alain Schonbrodt (Union Professionnelle Vétérinaire), Anne Simon (BAPCOC, UCL), Nathalie Stallaert (Vlaams Agentschap Zorg en Gezondheid), Nele Steens (FAGG – AFMPS), Carl Suetens (European Centre for Disease Prevention and Control (ECDC)), Léonard Théron* (Union Professionnelle Vétérinaire, HIPRA), David Tuerlinckx (UCL Mont Godinne), Koenraad Vandewoude (Kabinet Minister van Sociale Zaken en Volksgezondheid, UZ Gent), Stijn Van Hoestenbergh (Omegabaars), Piet Vanthemsche (Ex-FAGG, Ex-FAVV), Eline Vandael (Sciensano), Bill Vandaele* (Union Professionnelle Vétérinaire (UPV), HIPRA), Christelle Vercheval (CHU Liège), Bart Vergote (Pig farmer), Katie Vermeersch* (FAVV – AFSCA), Ann Versporten (BAPCOC, UAntwerpen), Dirk Vogelaers (Belgische Vereniging voor Infectiologie en Klinische Microbiologie (BVIKM – SBIMC), UZ Gent), Marjan Willaert* (pharma.be), Dominique Wouters (Association Belge des Pharmaciens Hospitaliers, UCL)

*: attended also the stakeholder meeting



Other external experts who attended the stakeholder meeting:

Virginie Bedoret (Société Scientifique de Médecine Générale (SSMG)), Caroline Briquet (Association Francophone Des Pharmaciens Hospitaliers De Belgique (AFPHB)), Association Belge des Pharmaciens Hospitaliers (BVZA), Cliniques universitaires Saint-Luc, Bruxelles), Jean-Pierre Bronckaers (Landsbond van Liberale Mutualiteiten), Lawrence Cuvelier (Groupement Belge des Omnipraticiens (GBO), Cartel), Antoon Daneels (Medaxes), Martine Delanoy (SPF Santé Publique, Sécurité de la Chaîne Alimentaire et Environnement – FOD Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu), Pierre Drielsma (Groupement Belge des Omnipraticiens (GBO), Cartel), Thibaut Dujardin (Union Nationale des Mutualités Socialistes), Laure Geslin (FAGG – AMPS), Els Goossens (Boerenbond), Claire Huyghebaert (Union Nationale des Mutualités Libres), Frank Koenen (Sciensano), Jacques Mainil (ULiège), Ludo Muls (IVDB dierenartsenbelangen – Dierenartsen in de VoedselKeten (DVK)), Alexandra Panis (Ministère de l'environnement wallon), Fabrice Peters (CSS – HGR), Annette Schuermans (BAPCOC – Federaal Platform voor ziekenhuishygiëne), Nathalie Shodu (Agence pour une Vie de Qualité (AVIQ)), Annik Simon (Cabinet du Ministre des Classes moyennes, des Indépendants, des PME, de l'Agriculture, et de l'Intégration sociale, chargé des Grandes villes), Leonard Théron (Union Professionnelle Vétérinaire (UPV)), Christiaan Van Haecht (Landsbond der Christelijke Mutualiteiten (LCM)), Emmanuel Wart (Cabinet du Ministre des Classes moyennes, des Indépendants, des PME, de l'Agriculture, et de l'Intégration sociale, chargé des Grandes villes)

External validators:

Corinne Bouuaert (ULiège), Pieter De Puydt (UGent), Katharina Staerk (Royal Veterinary College, University of London)

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Reported interests:

Membership of a stakeholder group on which the results of this report could have an impact (in addition to the affiliations mentioned above): Boudewijn Catry (BAPCOC & AMCRA), An De Sutter (Domus Medica), Pierre Drielsma (Fédération des maisons médicales et des collectifs de santé francophones (FMM)), Laure Geslin (Pharmacy association Brussels), Koen Magerman (Verbond van Belgische Artsen Specialisten (VBS)), Léonard Théron (HIPRA Benelux NV), Eline Vandael (BAPCOC)

Holder of intellectual property: Jeroen Dewulf (Developer Biocheck.UGent)

Fees or other compensations for writing a publication or participating in its development: Léonard Théron (Financing Walloon region, Project LAECEA)

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Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact (in addition to the affiliations mentioned above): Boudewijn Catry (EMA Antimicrobial Working Party), Els Goossens (Board member AMCRA), Davy Persoons (Administrator AMCRA), Léonard Théron (Founder of the veterinary technical network objective milk (RTVOL))

Layout:

Ine Verhulst, Joyce Grijseels

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■ TABLE OF CONTENTS

LIST OF FIGURES	8
LIST OF TABLES.....	10
LIST OF ABBREVIATIONS	13
■ SCIENTIFIC REPORT	23
1 INTRODUCTION.....	23
1.1 SHORT DESCRIPTION OF THE PROBLEM	23
1.1.1 Antibiotic resistance	23
1.1.2 Antibiotic use in Belgium.....	24
1.1.3 The concept of prudent antimicrobial/antibiotic use	24
1.1.4 One Health approach.....	24
1.1.5 Belgian Antibiotic Policy Coordination Committee (BAPCOC)	24
1.1.6 Difficult to obtain significant improvements.....	24
1.2 RESEARCH QUESTIONS & SCOPE	25
1.3 TERMINOLOGY	25
1.4 METHODOLOGY	26
1.5 STRUCTURE OF THE REPORT	26
2 ANTIBIOTIC USE AND ITS LINK WITH ANTIBACTERIAL RESISTANCE	27
2.1 WHAT IS ANTIMICROBIAL RESISTANCE?	27
2.1.1 Antibacterial resistance, a natural phenomenon	27
2.1.2 How do bacteria become resistant?	27
2.1.3 How does antibiotic resistance spread?	28
2.1.4 Multidrug resistant organisms.....	28
2.1.1 Resistance in community and healthcare acquired infections.....	29



2.2	WHAT IS PRUDENT ANTIBIOTIC USE?	29
2.3	USE AND MISUSE OF ANTIBIOTICS	30
2.4	THE BURDEN OF ANTIBACTERIAL RESISTANCE	30
2.5	TIME FOR ACTION.....	32
3	ANTIBIOTICS IN BELGIUM	33
3.1	WHO CAN PRESCRIBE ANTIBIOTICS IN BELGIUM?	33
3.1.1	Human sector.....	33
3.1.2	Veterinary sector.....	34
3.2	WHO CAN OBTAIN ANTIBIOTICS IN BELGIUM AND HOW?	34
3.2.1	Human sector.....	34
3.2.2	Who can administer antibiotics to animals and who is allowed to keep stocks of medicines at farms?.....	35
3.3	FINANCIAL ASPECTS.....	36
3.3.1	Human sector.....	36
3.3.2	Veterinary sector.....	42
3.4	ACTORS INVOLVED, INSPIRED BY THE VIABLE SYSTEMS MODEL	43
3.4.1	Introduction	43
3.4.2	Human sector.....	43
3.4.3	Veterinary sector.....	50
4	ANTIBIOTIC USE AND ANTIMICROBIAL RESISTANCE	54
4.1	HOW TO MEASURE ANTIBIOTIC USE	54
4.1.1	Human sector.....	54
4.1.2	Veterinary sector.....	59
4.2	HOW IS ANTIBIOTIC USE MONITORED?	61
4.2.1	Human sector.....	61



4.2.2	Veterinary sector	65
4.3	DATA ON ANTIBIOTIC USE IN BELGIUM, IN A EUROPEAN CONTEXT	68
4.3.1	Human sector	68
4.3.2	Veterinary sector	84
4.4	ANTIBIOTIC USE IN THE BELGIAN AMBULATORY AND HOSPITAL SECTOR FURTHER EXPLORED	90
4.4.1	Methods	90
4.4.2	Results	92
5	DETERMINANTS OF ANTIBIOTIC PRESCRIPTION AND USE.....	104
5.1	DETERMINANTS OF ANTIBIOTIC PRESCRIBING IN HUMAN MEDICINE	104
5.1.1	Determinants of antibiotic prescription in Belgium.....	105
5.1.2	Determinants of antibiotic prescription in other regions.....	110
5.1.3	Determinants of antibiotic use by patients	116
5.1.4	Limitations	119
5.2	DETERMINANTS OF ANTIBIOTIC PRESCRIPTION AND CHOICE IN VETERINARY MEDICINE	120
5.2.1	Methods	120
5.2.2	Determinants of antibiotic prescription.....	121
5.2.3	Determinants of antibiotic choice	126
5.2.4	Limitations	127
6	INTERVENTIONS TO PROMOTE THE PRUDENT USE OF ANTIBIOTICS	128
6.1	INTERVENTIONS TO PROMOTE THE PRUDENT USE OF ANTIBIOTICS IN THE HUMAN SECTOR.....	128
6.1.1	Belgian interventions to promote the prudent use of antibiotics	128
6.1.2	Interventions that have been implemented and evaluated elsewhere	153



6.2	INTERVENTIONS TO PROMOTE THE PRUDENT USE OF ANTIBIOTICS IN THE VETERINARY SECTOR	167
6.2.1	Introduction	167
6.2.2	Nation-wide interventions to promote prudent antibiotic use	169
6.2.3	European initiatives.....	173
6.2.4	Concluding remarks	173
6.2.5	Examples from abroad.....	173
6.3	OTHER ASPECTS TO CONSIDER IN DEVELOPING INTERVENTIONS AIMING TO CHANGE PRESCRIPTION BEHAVIOUR	177
7	STAKEHOLDER CONSULTATION AND SYSTEMS MAPPING	178
7.1	INTRODUCTION.....	178
7.2	APPROACH	178
7.3	SYSTEMS MAP	180
7.3.1	Concept and syntax of the systems map developed in this research	180
7.3.2	The status of the systems map.....	181
7.3.3	Use of systems maps.....	182
7.4	METHODS	184
7.4.1	Selection of stakeholders.....	184
7.4.2	Interview guide	184
7.4.3	Coding of interviews.....	185
7.4.4	Internal review of the systems map	186
7.4.5	Stakeholder review of the systems map	187
7.4.6	Stakeholder deliberation on suggested improvements of antibiotics policy	187
7.5	FINDINGS	187
7.5.1	Main features of the systems map	187



7.5.2	Description and presentation of the systems map.....	190
7.5.3	Assessment of the scope of the systems map	219
7.5.4	Stakeholders' suggestions to improve antibiotic policy, prescription and use	220
7.6	DISCUSSION	230
7.7	CONCLUSION	232
8	OTHER CHALLENGES WITH REGARD TO ANTIBIOTIC POLICY IN BELGIUM	233
8.1	ACCESS TO THE RIGHT ANTIBACTERIAL PRODUCT NOT STRAIGHTFORWARD	233
8.1.1	Background	233
8.1.2	The availability of antibiotics in Belgium	235
8.2	MISMATCH BETWEEN ANTIBIOTIC PACKAGE SIZE AND GUIDELINES FOR THEIR USE LEADING TO SELF-MEDICATION.....	238
8.3	ETHICAL CHALLENGE: INDIVIDUAL VS. COLLECTIVE RESPONSIBILITY	241
9	JOINT EC – ECDC ONE HEALTH COUNTRY VISIT TO BELGIUM – KEY ISSUES WITH REGARD TO ANTIBIOTIC USE.....	242
9.1	HUMAN HEALTH – ECDC	242
9.1.1	Observations made by ECDC.....	242
9.1.2	Key recommendations made by ECDC	245
9.2	ANIMAL HEALTH - DG HEALTH AND FOOD SAFETY.....	247
9.2.1	Observations made by DG Health and Food Safety	247
9.2.2	Considerations for possible future actions.....	250
10	DISCUSSION	251
11	HOW CAN THE SITUATION BE IMPROVED?.....	253
11.1	DEVELOP A NATIONAL ONE HEALTH AMR ACTION PLAN.....	253
11.2	STRENGTHEN ANTIBIOTIC STEWARDSHIP IN ACUTE CARE HOSPITALS	254
11.3	ROLL OUT LOCAL ANTIBIOTIC STEWARDSHIP TEAMS IN THE AMBULATORY SECTOR	255



11.4	DEVELOP ANTIBIOTIC STEWARDSHIP IN NURSING HOMES	255
11.5	IMPROVE THE PROFESSIONAL EDUCATION ON PRUDENT ANTIBIOTIC PRESCRIPTION AND USE, AND DEVELOP AND IMPLEMENT INTERVENTIONS TARGETING PSYCHOLOGICAL, SOCIAL AND INSTITUTIONAL DETERMINANTS OF BEHAVIOURAL CHANGE	256
11.6	RECOGNISE MEDICAL MICROBIOLOGY AND INFECTIOLOGY AS MEDICAL SPECIALTY AND PROVIDE REMUNERATION FOR THEIR ADVICE	257
11.7	IMPROVE THE AVAILABILITY OF OLD/NARROW SPECTRUM ANTIBIOTICS.....	257
11.8	PUT INTO PRACTICE THE DELIVERY OF THE EXACT NUMBER OF ANTIBIOTIC TABLETS IN PHARMACIES OPEN TO THE PUBLIC	258
11.9	IMPROVE THE COMPLIANCE WITH EVIDENCE-BASED PRESCRIPTION GUIDELINES	258
11.10	MAKE USE OF THE (FUTURE) MANDATORY IMPLEMENTATION OF E-PRESCRIBING TO IMPROVE THE PRUDENT PRESCRIPTION OF ANTIBIOTICS	259
11.11	CONSIDER TAKING STRUCTURAL MEASURES TO IMPROVE THE PRUDENT PRESCRIPTION AND USE OF ANTIBIOTICS.....	259
11.12	PERFORM A HEALTH TECHNOLOGY ASSESSMENT ON POINT-OF-CARE TESTING FOR THE DIAGNOSIS OF INFECTIOUS DISEASES IN THE BELGIAN AMBULATORY CARE CONTEXT	259
11.13	STIMULATE BEHAVIOURAL CHANGE AMONG THE GENERAL PUBLIC AS WELL AS THE PRESCRIBERS TOWARDS MORE PRUDENT USE OF ANTIBIOTICS	260
11.14	STRENGTHEN VETERINARIANS' COUNSELLING ROLE.....	260
11.15	CHANGE PRESCRIBING BEHAVIOUR OF HIGH ANTIBIOTIC PRESCRIBERS	261
11.16	MONITOR AND STIMULATE RESEARCH ON ANTIBIOTIC USE AND AMR IN THE SECTOR OF COMPANION ANIMALS	261
11.17	STIMULATE BIOSECURITY IMPROVEMENTS AS AN ALTERNATIVE TO ANTIBIOTIC USE.....	262
11.18	ENFORCE COMPLIANCE WITH THE LEGISLATION ON ANIMAL WELFARE	262
11.19	MAKE THE USE OF ANTIBIOTICS AS MEANS TO INTENSIFY ANIMAL PRODUCTION SUPERFLUOUS	263



11.20	AVOID SELF-MEDICATION BY MINIMIZING STOCKS AT FARMS AND BY ADJUSTING PACKAGE SIZES.....	263
11.21	DEFINE NEW GOALS REGARDING ANTIBIOTICS IN THE VETERINARY SECTOR.....	264
■	REFERENCES.....	265
■	APPENDICES	297
	APPENDIX 1. DETERMINANTS OF ANTIBIOTIC PRESCRIPTION AND USE IN HUMANS	297
	APPENDIX 1.1. SUMMARY OF METHODS FOR LITERATURE SEARCH.....	297
	APPENDIX 1.2. CHARACTERISTICS OF INCLUDED BELGIAN STUDIES AND REVIEWS	299
	APPENDIX 2. DETERMINANTS OF ANTIBIOTIC PRESCRIPTION AND CHOICE IN VETERINARY MEDICINE.....	302
	APPENDIX 2.1. SEARCH STRATEGY	302
	APPENDIX 3. LITERATURE REVIEW OF INTERVENTIONS THAT HAVE BEEN IMPLEMENTED ELSEWHERE	304
	APPENDIX 3.1. SEARCH STRATEGY OF INTERVENTIONS THAT HAVE BEEN IMPLEMENTED ELSEWHERE.....	304
	APPENDIX 3.2. REFERENCES CONSIDERED FOR THE CHAPTER ON INTERVENTIONS THAT HAVE BEEN IMPLEMENTED ELSEWHERE.....	305
	APPENDIX 4. QUESTIONS USED IN THE INTERVIEW GUIDE	347
	APPENDIX 4.1. KEY QUESTIONS FOR INTERVIEWEES FROM THE HUMAN (AMBULATORY AND HOSPITAL) SECTOR	347
	APPENDIX 4.2. ADDITIONAL QUESTIONS FOR INTERVIEWEES FROM THE AMBULATORY SECTOR	347
	APPENDIX 4.3. ADDITIONAL QUESTIONS FOR INTERVIEWEES FROM THE HOSPITAL SECTOR.....	348
	APPENDIX 4.4. KEY QUESTIONS FOR INTERVIEWEES FROM THE VETERINARY SECTOR.....	348
	APPENDIX 5. SYSTEMS MAP.....	350
	APPENDIX 5.1. CONCEPTS.....	350
	APPENDIX 5.2. CONNECTIONS BETWEEN CONCEPTS.....	359
	APPENDIX 5.3. ASSESSMENT OF THE SCOPE OF THE SYSTEMS MAP	374



LIST OF FIGURES

Figure 1 – Total health insurance expense for all medicines, 2011-2017**	36
Figure 2 – Total health insurance expense for antibiotics, 2011-2017**	37
Figure 3 – Evolution of the health insurance expense for antibiotics per 1000 inhabitants per day by ATC 4 class, 2011-2017**	38
Figure 4 – The viable systems model applied to the human sector	44
Figure 5 – The viable systems model applied to the veterinary sector	50
Figure 6 – Use of antibiotics for systemic use in the ambulatory sector by antibiotic group, EU/EEA countries, 2015 (Left: expressed in DDD per 1000 inhabitants and per day; right: expressed as packages per 1000 inhabitants and per day)	57
Figure 7 – Trends in the use of antibacterials for systemic use (ATC group J01), expressed with the 2018 ATC/DDD index and the 2019 ATC/DDD index, 2007-2017	69
Figure 8 – Use of antibiotics (ATC group J01) in the ambulatory sector in Europe, 2017	70
Figure 9 – Trend in the use of antibiotics for systemic use (ATC group J01) in the Belgian ambulatory sector expressed as DDD per 1000 inhabitants per day, 1997 – 2017	71
Figure 10 – The use of antibiotics in the hospital sector by antibiotic group, EU/EEA countries, 2017, expressed as DDD per 1000 inhabitants and per day	74
Figure 11 – Trend in the use of antibiotics (ATC group J01) in the Belgian hospital sector expressed as DDD per 1000 inhabitants per day, 1997-2017	75
Figure 12 – Total national use of antibacterial compounds for veterinary use in Belgium for the years 2007-2017, expressed as tons active substance	84
Figure 13 – Distribution of sales of veterinary antimicrobial agents for food-producing animals, in mg of active substance per population correction unit ^b (mg/PCU), by pharmaceutical form in 30 European countries for 2016	87
Figure 14 – Total sales of veterinary antimicrobial agents for food-producing species, in mg/PCU, from 2010 to 2016, for 30 European countries	88
Figure 15 – Spatial distribution of overall sales of all antimicrobials for food-producing animals, in mg/PCU, for 30 countries, for 2016	89



Figure 16 – Number of DDD per 1000 inhabitants per day (DID), by province of the prescriber, 2016.....	94
Figure 17 – Proportion of the total DDD in the ambulatory sector, by ATC code, 2016	96
Figure 18 – Ratio broad to narrow spectrum antibiotics, by province of the prescriber, 2016	98
Figure 19 – Evolution of antibiotic use in DDD/1000 inhabitants/day in cities, 2000-2016, France	165
Figure 20 – Evolution of antibiotic hospital use in DDD/1000 inhabitants per day (left) and DDD/1000 hospitalization days (right), 2000-2016, France	166
Figure 21 – Antimicrobial veterinary medicinal product sales in the Netherlands, 1999-2017	175
Figure 22 – An influence link between two concepts	180
Figure 23 – Positive, negative and neutral connections between concepts.....	181
Figure 24 – Data collection process	186
Figure 25 – Core of the systems map - part 1	192
Figure 26 – Core of the systems map – part 2	193
Figure 27 – Stewardship teams in hospitals.....	195
Figure 28 – Antibiotic policy.....	197
Figure 29 – Sensitisation campaigns.....	198
Figure 30 – Antibiotic prescription guidelines (human)	200
Figure 31 – Antibiotic prescription guidelines (veterinary).....	201
Figure 32 – Practitioner expertise and reflexivity	204
Figure 33 – Ambulatory practitioner-patient relationship.....	206
Figure 34 – Market of antibiotics	208
Figure 35 – Veterinary sector autoregulation	210
Figure 36 – Farmers	213
Figure 37 – Livestock business model 1	215
Figure 38 – Livestock business model 2	216
Figure 39 – Veterinarians' antibiotic prescription practices	218



Figure 40 – Veterinary sector regulation	219
Figure 41 – Selection of references.....	303

LIST OF TABLES

Table 1 – Burden of AMR on population health – estimates for 2015-2050	32
Table 2 – Drug reimbursement categories B and C and patients' share in 2018.....	39
Table 3 – Number of DDD per package	58
Table 4 – Drug-specific quality indicators for outpatient antibiotic use in Europe, results for Belgium in 2017.....	72
Table 5 – Prevalence of antimicrobial use in hospitals in Belgium and the EU/EEA, 2016-2017 ECDC PPS	73
Table 6 – Indications for antimicrobial use in Belgium and the EU/EEA, 2016-2017 ECDC PPS	76
Table 7 – Most commonly used antimicrobials by indication in Belgium and the EU/EEA, 2016-2017 ECDC PPS	77
Table 8 – Site of infection for which antimicrobial treatment is indicated in Belgium and the EU/EEA, 2016-2017 ECDC PPS.....	78
Table 9 – Prevalence of antimicrobial use in nursing homes in Belgium and the EU/EEA, 2016-2017 ECDC PPS	79
Table 10 – Use of antibiotics (ATC group J01) in nursing homes in 2016-2017	80
Table 11 – Ways of obtaining antibiotics in Belgium and the 28 EU member states in 2016	81
Table 12 – Reasons for taking antibiotics in Belgium and the 28 EU member states in 2016.....	82
Table 13 – Overall knowledge about antibiotics in Belgium and the 28 EU member states in 2016	83
Table 14 – Sales of the various antimicrobial classes for food-producing animals in 2016.....	86
Table 15 – Indicators for any antibiotic use (ATC group J01) in the ambulatory sector, by year.....	92
Table 16 – Proportion of inhabitants with at least one antibiotic delivered, by patient characteristics, 2016	93
Table 17 – Antibiotic use in the ambulatory sector in DID and TID, by age-group of the patient, 2016	93
Table 18 – Use of any antibiotic (ATC group J01) in the ambulatory sector, by province of the prescriber, 2016.....	94



Table 19 – Antibiotic use in the ambulatory sector, by type of prescriber, 2016	95
Table 20 – Antibiotic use in the ambulatory sector, by age group of the prescriber, 2016	95
Table 21 – Antibiotic use in the ambulatory sector per ATC code, in proportion of total antibiotic use in DDD, by age-group, 2016	96
Table 22 – Penicillins (J01C) use in 0 to 14 years per ATC code, in proportion of total penicillin use in DDD, 2016.....	97
Table 23 – Use of other antibacterials (J01X) in the ≥ 65 age group, 2016.....	97
Table 24 – Proportion quinolone of the total DDD in the ambulatory sector, by province of the prescriber, 2016	97
Table 25 – Ratio* broad to narrow spectrum antibiotics in the ambulatory sector, by year and age-group	98
Table 26 – Ratio amoxicillin to amoxicillin-clavulanate in the ambulatory sector, by year and age-group	98
Table 27 – Proportion generic antibiotics out of the total DDD per ATC code, in the ambulatory sector, 2016	99
Table 28 – Antibiotic use in the hospital sector, by year, 2014-16.....	99
Table 29 – Antibiotic use in the hospital sector, by age-group of the patient, 2016.....	100
Table 30 – Antibiotic use in the hospital sector, by ward, 2016	100
Table 31 – Antibiotic use in the hospital sector, by ATC code, 2016	101
Table 32 – Antibiotic use in the hospital sector in proportion of total antibiotic DDD, by ATC code and by age-group of the patient, 2016.....	102
Table 33 – Proportion of broad-spectrum antibiotic use in the hospital sector, by ward, 2016.....	102
Table 34 – Ratio amoxicillin to amoxicillin-clavulanate in the hospital sector, by year	103
Table 35 – Antibiotic use in the hospital sector, proportion generic by ATC code, 2016.....	103
Table 36 – Determinants of antibiotic prescription in Belgian studies.....	105
Table 37 – Determinants for antibiotic use related to the prescriber.....	112
Table 38 – Determinants for antibiotic use related to the health care system	113
Table 39 – Determinants for antibiotic use related to the patient and its environment	115



Table 40 – Determinants for antibiotic adherence and self-medication	118
Table 41 – Determinants of veterinary antibiotic prescription and use	122
Table 42 – Overview of determinants of antibiotic choice	126
Table 43 – BAPCOC evaluation of the implementation of antibiotic stewardship initiatives (%) in the acute care hospitals, 2007-2011	131
Table 44 – National guidelines for prudent antibiotic prescription and use at human level	148
Table 45 – Interventions for prudent antibiotic prescription and veterinary use	168
Table 46 – Operational goals and their status	169
Table 47 – Clusters and key concepts of the systems map	188
Table 48 – Output of the ambulatory care subgroup	221
Table 49 – Output of the hospital care subgroup	225
Table 50 – Output of the veterinary subgroup	228
Table 51 – Examples of temporary supply problems and marketing cessations of antibiotics in Belgium (2013 – 2018)	236
Table 52 – Examples of mismatches between antibiotic packaging and guidelines for their use	239
Table 53 – Characteristics of studies describing determinants for antibiotic prescription in Belgium	299
Table 54 – Characteristics of literature reviews describing determinants for antibiotic prescription	300
Table 55 – Characteristics of studies describing determinants for antibiotic compliance and self-medication	300
Table 56 – Concepts included in the systems map	350
Table 57 – Connections between concepts in the systems map	359
Table 58 – Determinants of human antibiotic use identified in the literature and related concepts in the systems map	374
Table 59 – Determinants of veterinary antibiotic use identified from the literature and related concepts in the systems map	375
Table 60 – Determinants of veterinary antibiotic choice identified from the literature and related concepts in the systems map	378



LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AB(s)	Antibiotic(s)
ABR	Antibacterial Resistance
ABS	Farmers' union ('Algemeen Boerensyndicaat')
ABSt	Antibiotic Stewardship
ABStT	Antibiotic Stewardship teams
ABUH (project)	Antibiotic Use in Hospitals (project)
AFPHB	French speaking Association of Hospital Pharmacists from Belgium ('Association Francophone des Pharmaciens Hospitaliers de Belgique')
AGISAR	WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AMC	Antimicrobial Medicines Consumption
AMCRA	Belgian Centre of Expertise on Antimicrobial Consumption and Resistance in Animals
AMR	Antimicrobial Resistance
AMT	Antimicrobial Management Team
AMU	Antimicrobial Use
AP	Ambulatory Practitioner
API	Active Pharmaceutical Ingredient
APQI	Antibiotic Prescribing Quality Indicator
APR-DRG	All Patient Refined Diagnosis Related Group
ARSIA	Animal health association ('Association Régionale de Santé et d'Identification Animale')
ASP	Antimicrobial Stewardship Program
AST	Antibiotic Sensitivity Testing
ATC	Anatomical Therapeutic Chemical (classification)



ATCvet	Anatomical Therapeutic Chemical Classification System for veterinary medicinal products
AVMP	Antimicrobial Veterinary Medicinal Product
BAPCOC	Belgian Antibiotic Policy Coordination Committee
BB	Farmers' union ('Boerenbond')
BCV	Belgian Controlled Veal (quality program installed by the professional union for veal calves farmers)
BeH-SAC	Belgian Hospitals - Surveillance of Antimicrobial Consumption
BelVet-Sac	Belgian Veterinary Surveillance of Antimicrobial Consumption
BFA	Belgian Feed Association
BFM	Budget of Financial Means ('Budget van Financiële Middelen'/'Budget des Moyens Financiers')
BIGAME	AB use registry for the Walloon region ('Base Informatique de Gestion des Antibiotiques et des Médicaments en Elevage')
BSI	Bloodstream Infection
BVIKM – SBIMC	Belgian society for infectiology and clinical microbiology ('Belgische Vereniging voor Infectiologie en Klinische Microbiologie'/'La Société Belge d'Infectiologie et de Microbiologie Clinique')
BVK	Professional union for Belgian veal calf producers ('Beroepsvereniging voor de Belgische Kalfsvleessector vzw')
CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance
CBA	Control Before After
CDC	Centers for Disease Control and Prevention (US)
CDI	<i>Clostridium difficile</i> Infections
CDSS	Computerized/clinical Decision Support System
CI	Confidence Interval
CIA	Critically Important Antimicrobial



CLABSI	Central Line Associated Bloodstream Infection
CLSI	Clinical & Laboratory Standards Institute
CME	Continuous Medical Education
CNK	Ordering number attributed to all medicines and parapharmaceutical products ('Code nation(a)al kodenummer')
CODA – CERVA	Veterinary and agrochemical research centre ('Centrum voor Onderzoek in Diergeneeskunde en Agrochemie' – 'Centre d'Études et de Recherches Vétérinaires et Agrochimiques')
COPD	Chronic Obstructive Pulmonary Disease
CPD	Continuous Professional Development
CPE	Carbapenemase Producing Enterobacteria
CRA – MCC	Coordinating and advising physician ('Coördinerend Raadgevend Arts'/'Médecin Coordinateur et Conseiller')
CRBSI	Central Line Related Bloodstream Infection
CRE	Carbapenem-Resistant Enterobacteriaceae
CRP	C-Reactive Protein
CTG – CRM	Commission for the reimbursement of pharmaceuticals ('Commissie Tegemoetkoming Geneesmiddelen'/'Commission de Remboursement des Médicaments')
DAF	Administration and provision document ('Document d'Administration et de Fourniture')
DALY	Disability-Adjusted Life Year(s)
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Programme
DCDvet	Defined Course Dose for Animals
DDD	Defined Daily Dose
DDDvet	Defined Daily Dose for Animals
DG	Directorate-General



DGZ	Animal health care Flanders ('Dierengezondheidszorg Vlaanderen')
DID	Defined Daily Dose (DDD) per 1000 Inhabitants per Day
DQA	Dairy Quality Assurance
DRD	Defined Daily Doses (DDD) per 1000 Residents per Day
DRIVA-AB	Driving Reinvestment In Research and Development and Responsible Antibiotic use
EAAD	European Antibiotic Awareness Day
EARS-Net	European Antimicrobial Resistance Surveillance Network
EARSS	European Antimicrobial Resistance Surveillance System
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EFSA	European Food Safety Authority
EFTA	European Free Trade Association
EMA	European Medicines Agency
EPOC	Effective Practice and Organisation of Care
EPRUMA	European Platform for the Responsible Use of Medicines in Animals
ESAC	European Surveillance of Antimicrobial Consumption
ESAC-NH	European Surveillance of Antimicrobial Consumption in Nursing Homes
ESAP	European Strategy for Antibiotic Prophylaxis
ESBL	Extended-Spectrum Beta-Lactamase producing Bacteria
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESGAP	ESCMID Study Group for Antibiotic Policies
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EU	European Union



EUCAST	European Committee on Antimicrobial Susceptibility Testing
EUMS	European Union of Medical Specialities
FAGG – AFMPS	Federal Agency for Medicines and Health Products ('Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten'/'Agence Fédérale des Médicaments et Produits de Santé')
FAO	Food and Agriculture Organization (of the United Nations)
FAVV – AFSCA	Federal Agency for the Safety of the Food Chain ('Federaal Agentschap voor de veiligheid van de voedselketen'/'Agence Fédérale pour la Sécurité de la Chaîne Alimentaire')
FIDIN	Dutch association of producers and importers of veterinary medicines ('Fabrikanten Importeurs Dierengeneesmiddelen Nederland')
FOD VVVL – SPF SPSCAE	Federal Public Service Health, Food Chain Safety and Environment ('Federale overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu'/'Service public fédéral Santé publique, Sécurité de la Chaîne Alimentaire et Environnement')
FTE	Full Time Equivalent(s)
FVE	Federation of Veterinarians of Europe
FWA	Farmers' union ('Fédération Wallonne de l'Agriculture')
GBS	Group B Streptococcus
GDP	Gross Domestic Product
GP	General Practitioner
GRACE INTRO	Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe/INternet Training for Reducing antibiOTic use
GUI	Genitourinary Tract Infection
HA-BSI	Hospital-Associated Bloodstream Infection
HAI	Healthcare-Associated Infection
HAI-Net	Healthcare-Associated Infections Surveillance Network



HALT	Healthcare-Associated Infections in Long-Term Care Facilities
HAO	Haematology and/or Oncology unit
HELICS	Hospitals in Europe Link for Infection Control through Surveillance
HGR – CSS	Superior Health Council ('Hoge Gezondheidsraad'/'Conseil Supérieur de la Santé')
HGT	Horizontal Gene Transfer
HIS	Health Interview Survey
ICPC	International Classification of Primary Care
ICPC-2-R	Revised second edition of International Classification of Primary Care
ICU	Intensive Care Unit
IGGI	Infection guide ('Infectiologiegids' – 'Guide d'Infectiologie')
IKB	Quality assessment system ('Integrale Keten Beheersing')
IKM – QFL	Quality label for dairy farming ('Integrale Kwaliteitszorg Melk'/'Qualité Filière Lait')
ILI	Influenza-Like Illness
IMA – AIM	Intermutualistic Agency ('Intermutualistisch Agentschap'/'Agence Intermutualiste')
IMI	Innovative Medicines Initiative
INN	International Non-proprietary Name ('Voorschrift op Stofnaam' (VOS) / 'Dénomination Commune Internationale' (DCI))
IPC	Infection Prevention and Control
IPSE	Improving Patient Safety in Europe
IQR	Interquartile Range
IT	Information Technology
ITS	Interrupted Time Series
IV	Intravenous
JCI	Joint Commission International



KCE	Belgian Health Care Knowledge Centre ('Federaal Kenniscentrum voor de Gezondheidszorg'/'Centre Fédéral d'Expertise des Soins de Santé')
LA-MRSA	Livestock-Associated Methicillin-Resistant <i>Staphylococcus Aureus</i>
LOK – GLEM	Local Quality Circle ('Lokale Kwaliteitsgroep'/'Groupe Local D'évaluation Médicale')
LOS	Length of Stay
LQAS	Lot Quality Assurance Sampling
LRTI	Lower Respiratory Tract Infection
LTCF	Long-Term Care Facility
MARAN	Monitoring of Antimicrobial Resistance and Antibiotic usage in Animals in the Netherlands
MD	Medical Doctor
MDR(O)	Multidrug-Resistant (Organisms)
MIC	Minimal Inhibitory Concentration
MIT	Multidisciplinary Infectious diseases Team
MLS	Macrolides, Lincosamides And Streptogramins
MRSA	Methicillin-Resistant <i>Staphylococcus Aureus</i>
NA	Not Available
NCQP	National Council for Quality Promotion
NGROD	Dutch speaking supreme council of the order of veterinarians ('Nederlandstalige Gewestelijke Raad van de Orde der Dierenartsen')
NH	Nursing Home
NIAZ	Nederlands Instituut voor Accreditatie in de Zorg
NRS	Non-Randomised Studies
NUTS	Nomenclature of Territorial Units for Statistics
OECD	Organisation for Economic Co-operation and Development



OIE	World Organisation for Animal Health ('Office International des Epizooties')
OR	Odds Ratio
P4P	Pay-For-Performance
PAP	Perioperative Surgical Prophylaxis
PAR	Post-Antibiotic Prescription Review
PCT	Procalcitonin
PCR	Polymerase Chain Reaction
PCU	Population Correction Unit
PDD	Prescribed Daily Dose
PDR	Pandrug-resistant (bacteria)
PID	Packages per 1000 Inhabitants per Day
PNSP	Penicillin Non-Susceptible <i>Streptococcus Pneumoniae</i>
PPP	Purchasing Power Parity
PPS	Point Prevalence Survey
PrID	Prescriptions per 1000 Inhabitants per Day
PTAM	Pharmacotherapy Audit Meeting
Q&S	Quality and Safety ('Qualität & Sicherheit')
QI	Quality Indicator
RCT	Randomised Controlled Trial
RD	Royal Decree
RIVM	Dutch National Institute for Public Health and the Environment ('Rijksinstituut voor Volksgezondheid en Milieu')
RIZIV – INAMI	National Institute for Health and Disability Insurance ('Rijksinstituut voor Ziekte- en Invaliditeitsverzekering'/'Institut National d'Assurance Maladie-Invalidité')
RR	Risk Ratio



RTI	Respiratory Tract Infection
SANITEL-MED	Belgian registry for antibiotic use in animals
SDa	The Netherlands veterinary medicines institute ('Stichting Autoriteit Diergeneesmiddelen')
SOI	Severity of Illness
SSI	Surgical Site Infection
SSMG	Scientific association of general practitioners ('Société Scientifique de Médecine Générale')
TCT	Technical Cell ('Technische Cel voor de verwerking van de gegevens met betrekking tot de ziekenhuizen'/'Cellule Technique de traitement de données relatives aux hôpitaux')
TESSy	The European Surveillance System (database)
TID	Treatment(s) per 1000 Inhabitants per Day
TRACE	Translational Research on Antimicrobial resistance and Community-acquired infections in Europe
TVD	Administration and provision document ('Toedienings- en verschaffingsdocument'/'Document d'administration et de fourniture')
UCL	Université catholique de Louvain
UGent	Ghent University
ULB	Université libre de Bruxelles
ULg	Université de Liège
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection
VASC	Veterinary Advisory Service Contracts
VIP ²	Quality improvement project in Flemish acute care hospitals ('Vlaams Indicatorenproject voor Patiënten en Professionals')
VMP	Veterinary Medicinal Product



VRE	Vancomycin-Resistant Enterococci
VSM	Viable Systems Model
VZW	Non-profit organization ('Vereniging zonder winstoogmerk')
WAAW	World Antibiotic Awareness Week
WHO	World Health Organization
WIV – ISP	Scientific Institute of Public Health ('Wetenschappelijk Instituut Volksgezondheid'/'L'Institut Scientifique de Santé Publique')
XDR	Extensively Drug-Resistant (Bacteria)
ZnO	Zinc oxide



■ SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Short description of the problem

1.1.1 *Antibiotic resistance*

Since the discovery of penicillin in 1928 and more precisely since its availability for medical use in the 1940s, the use of antibiotics has made major contributions to public health. Many of the improvements in mortality and morbidity that modern medicine has secured are for the greater part based on the ability to prevent and cure infections. The introduction of antimicrobial therapies (among which antibiotics) has, for example, markedly decreased the burden of infectious diseases (e.g. pneumonia and tuberculosis) and has allowed the introduction of complex medical interventions such as major surgery, organ transplantations and care of premature babies, by preventing hospital-acquired infections.¹

Yet systematic misuse and overuse of antimicrobial drugs in human medicine and animal husbandry has resulted in the emergence of resistance to these drugs, undermining many of the advances that were realised thanks to antimicrobial therapy. The direct consequences of infection with resistant microorganisms can be severe, including longer illnesses, increased mortality, prolonged hospital stays, lower protection for patients undergoing surgery and other medical procedures and increased costs.² The problem is even more pronounced when dealing with multidrug-resistant organisms (MDRO), as these are resistant to more than one antibiotic (e.g. *Acinetobacter* spp., with combined resistance to fluoroquinolones, aminoglycosides and carbapenems).

Antibiotic resistance severely limits the number of antibiotics available nowadays for the treatment of diseases. Few replacement products are in the pipeline. The World Health Organization (WHO) sets the picture clear: without harmonized and immediate action on a global scale, the world is heading towards a post-antibiotic era in which common infections could once again kill.² Antibiotic resistance is present in every country, also in Belgium.



The ultimate goal of controlling antimicrobial resistance can only be achieved by combining strong infection prevention and control (including vaccination) and the prudent use of antimicrobials. Infection prevention and control contributes to a decrease in the number of infections, which leads to lower antimicrobial prescription and use and fewer opportunities for misuse.³

1.1.2 Antibiotic use in Belgium

The amount of antibiotics used in Belgium depends on the sector. In the ambulatory sector (i.e. outside hospitals), Belgium scores badly with 27.5 defined daily doses^a (DDD) per 1 000 inhabitants and per day in 2016, while for instance in the Netherlands the respective figure was only 10.4.⁴ Belgium does better when it comes to the systemic use of antibiotics in the hospital sector: 1.63 DDD per 1000 inhabitants and per day in 2016, while the European Union (EU) and European Economic Area (EEA) population-weighted mean use was 2.06.⁴ In the veterinary sector 158.3 mg antimicrobial agents per population correction unit^b (PCU) were sold in Belgium in 2014. Across the 29 European countries, the sales of these products ranged from only 3.1 mg/PCU in Norway to 418.8 mg/PCU in Spain.⁵

1.1.3 The concept of prudent antimicrobial/antibiotic use

Given the fact that any use of antimicrobials can result in the development of antimicrobial resistance (AMR), but that this risk increases if antimicrobials are used in a non-prudent way (e.g. at sub-therapeutic doses, in an untargeted manner through mass medication or use on non-susceptible microorganisms), the prudent use of antimicrobials in both human and veterinary medicine is one of the main axes in tackling AMR. Prudent use of antimicrobials should lead to more rational and targeted use, thereby maximising the therapeutic effect and minimising the development of AMR.⁶

^a The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

1.1.4 One Health approach

The 'One Health' concept acknowledges that human health is interconnected with the health of animals and the environment. The goal of One Health is to encourage the collaborative efforts of multiple disciplines to achieve the best health for people, animals, and our environment. The One Health approach is a condition sine qua non in the battle against antibiotic resistance.

1.1.5 Belgian Antibiotic Policy Coordination Committee (BAPCOC)

In response to the high antibiotic use in the 90s - Belgium was in the top 3 of European countries - the Belgian Antibiotic Policy Coordination Committee (BAPCOC) was officially established in 1999. The overall objective of BAPCOC is to promote according to the One Health approach, the prudent use of antibiotics in humans and animals and to promote infection control and hospital hygiene, with the overall aim to reduce antibiotic resistance.⁷

1.1.6 Difficult to obtain significant improvements

Despite numerous initiatives taken at several levels (e.g. BAPCOC, RIZIV – INAMI, FOD VVVL – SPF SPSCAE, hospitals, ambulatory sector) and the large amount of money that is yearly spent on awareness about antibiotic prescribing and infection control, Belgium still ranks high in the use of antibiotics, especially in the ambulatory sector.⁸

^b The population correction unit is a proxy for the size of the food-producing animal population (including horses).



1.2 Research questions & scope

The present study was submitted by the Federal Public Service Health, Food Chain Safety and Environment (FOD VVVL – SPF SPSCAE), on behalf of the Belgian Antibiotic Policy Coordination Committee (BAPCOC). The study has four major research questions:

1. Which initiatives with respect to prudent antibiotic prescribing and the push back of antibacterial resistance have been taken since the establishment of BAPCOC in 1999, in the human and veterinary sector? Was their impact on reducing AMR evaluated?
2. What is the current situation of antibiotic use in Belgium?
3. What are the main drivers of these current patterns of antibiotic use?
4. Which strategies can improve the prudent use of antibiotics in Belgium?

The ultimate objective of the study is to formulate proposals and recommendations to promote the prudent use of antibiotics in the human and veterinary sector, to effectively reduce antibacterial resistance. Although infection prevention and control, hospital hygiene and prevention (e.g. vaccination) play a key role in the overall aim to reduce antibiotic resistance, these topics were considered out of scope for the present study.

The focus of the present study is **limited to antibiotics** (ATC^c group J01), i.e. antimicrobials with activity against bacteria; other antimicrobials like antifungals, antivirals and antiparasitics were not considered. Although infection control such as hospital hygiene and vaccination against non-susceptible pathogens play an important role in the overall reduction of antibiotic resistance, these topics were not included in the scope of the present study. Likewise, the development of new antibiotics, clinical trials and the research and development aspects, were not covered either.

Our report covers the **human as well as the veterinary sector**. Environmental issues were not considered either.

This report tackles two main issues: on the one hand the prescription of antibiotics, which depends on the decision of the physician and on the other hand the use of antibiotics by patients, which depends on the patient's decision. Indeed, not all prescribed antibiotics are taken by patients, and not all antibiotics taken by patients have been prescribed. Other elements than prescription are influencing the use of antibiotics by a population, and they relate to the patient behaviour, in particular the adherence to a prescribed treatment, and self-medication, i.e. intake of antibiotics that were not prescribed for that episode. In this report, the two levels of decision-making are distinguished, in particular when assessing the factors that influence each of them (Chapter 5 and Chapter 7).

1.3 Terminology

In the medical field the terms 'antibiotic use' and 'antibiotic consumption' alike are used; for the present report it was opted to use wherever possible the term 'antibiotic use'. Likewise, several synonyms have been used for 'prudent' use of antibiotics: e.g. 'appropriate', 'rational', 'judicious' and 'responsible'. In the European Union, the term "prudent use" is preferred, defined by the European Commission as a use which benefits the patient while at the same time minimises the probability of adverse effects and the emergence or spread of antimicrobial resistance.³ 'Prudent' is thus used with the same purpose as rational, adequate or correct use of antibiotics. In the remainder of this report, we refer to the 'prudent' use of antibiotics.

Further, we opted to use the term 'ambulatory care' or 'ambulatory sector' as a synonym to 'outpatient' or 'community'.

^c The Anatomical Therapeutic Chemical (ATC) Classification System is used for the classification of active substances of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.



1.4 Methodology

To answer the aforesaid research questions, the following research methods were applied:

- A review of the international literature, policy documents, national and international reports;
- The consultation of stakeholders, through face-to-face interviews, stakeholder workshops and a stakeholder meeting (see Colophon);
- The analysis of Belgian 2014-2016 reimbursement data on the use of antibiotics in the ambulatory and hospital sector;
- A review of this report by three independent scientific experts (see Colophon).

1.5 Structure of the report

In **chapter 2** we provide the reader with background information on antibiotic use and antibacterial resistance; more precisely we focus on the questions: what is antibacterial resistance, what is prudent antibiotic use, and what is the link between antibiotic use and antibacterial resistance?

Chapter 3 is devoted to the Belgian situation with regard to antibiotic prescription and use: who can prescribe antibiotics in Belgium, what are the financial aspects and which actors are involved? These questions are addressed separately for the human and veterinary sector.

In **chapter 4** we concentrate on the monitoring of antibiotic use in the human and veterinary sector and provide data for both sectors on antibiotic use in Belgium, in a European context. In this chapter we also pay attention to the measurement of antibiotic use and its challenges.

Chapter 5 is dedicated to the determinants that influence the prescription of antibiotics, in human and veterinary medicine. Determinants belong to various categories: factors related to the prescriber, to the patient, to the animal-owner, to the health care system or to the overall culture.

Chapter 6 gives an overview of the interventions to promote the prudent use of antibiotics and the push back of antimicrobial resistance in the human and veterinary sector in Belgium since 1999 (i.e. the establishment of BAPCOC).

But more importantly, the authors verified whether the listed interventions were also evaluated and what their impact was. In essence, this chapter gives an answer to research question 1.

In **chapter 7** the reader can find in detail how stakeholders were consulted in this research project and their analysis of the current situation with regard to antibiotic use and antibacterial resistance. This chapter focuses on the (human) ambulatory sector, the hospital sector and the veterinary sector.

In **chapter 8** we addressed some additional challenges with regard to the prudent use of antibiotics and antibacterial resistance, more precisely access to the right antibacterial product and the mismatch between antibiotics' pack size and guidelines for their use which leads to self-medication. The subjects were distilled from the interviews with stakeholders as well as from the literature reviews.

In November 2017, the European Centre for Disease Prevention and Control (ECDC) and the European Commission's Directorate-General (DG) for Health and Food Safety jointly carried out a country visit to Belgium to discuss antimicrobial resistance (AMR) issues; their main findings were summarised in two reports. In **chapter 9** we provide a summary of the most important findings of both reports, limited to the prudent use of antibiotics in Belgium, as this is the scope of the present report.

In **chapter 10** a brief discussion of the most important findings is provided.

In **chapter 11** we reflect on how the situation can be improved and formulate recommendations from the One Health perspective. In this chapter we provide answers to the fourth research question.



2 ANTIBIOTIC USE AND ITS LINK WITH ANTIBACTERIAL RESISTANCE

2.1 What is antimicrobial resistance?

2.1.1 Antibacterial resistance, a natural phenomenon

Antibacterial resistance is a **natural phenomenon**, which is part of the evolution of bacteria.¹ Any use of antibiotics has the potential to stimulate the development of resistance to it, as this is the natural response of bacteria.⁹ If a new trait results helpful for a bacterium's survival and reproduction, the lineage descending from that bacterium becomes more common by replacing, through natural selection, bacteria that did not inherit that trait.

Box 1 – Antibacterial versus antimicrobial resistance

Antibacterial resistance refers to the capacity of the bacteria to resist to the action of antibiotics, making them ineffective.

Antimicrobial resistance refers to the ability of any microorganism (not just bacteria but also viruses, parasites and fungi) to resist to antimicrobial treatments.

In animals or humans it may take millions of years before a new helpful trait becomes predominant, but in the case of unicellular microorganisms, like bacteria, this process is much shorter as they can reproduce as often as every 20 minutes. For example, ampicillin, which was discovered in 1958 and made available on the market in 1961, is now widely tolerated by many strains of microorganisms. Nearly 100% of hospital-acquired *Klebsiella* infections in developing countries are now ampicillin resistant.^{1, 10}

2.1.2 How do bacteria become resistant?

Some bacteria are **intrinsically resistant** to certain types of antibiotics. However, the main issue in antimicrobial resistance is the **acquisition of resistance in a bacterial population that was originally susceptible** to an antibacterial drug.

The **major driver** behind the development of antimicrobial resistance is the **non-prudent use of antimicrobial agents in both humans and animals**, by exerting ecological pressure on the bacteria.¹¹

The development of acquired resistance can be the result of mutations in chromosomal genes or by acquiring external genetic determinants of resistance such as plasmids, obtained from other resistant organisms present in the environment (Box 2).¹²

Box 2 – Mechanisms of acquired resistance

Acquired resistance through mutations

Like all living organisms, bacteria can go through random evolutionary changes in their genes. Mutations in these genes can produce new or altered traits that may provide new abilities or capacities. For instance, some mutations enable the bacteria to produce enzymes that inactivate antibiotics (e.g. beta-lactamase), other mutations eliminate the cell target that the antibiotic attacks, others close up the entry ports that allow antibiotics into the cell, and still others manufacture pumping mechanisms that export the antibiotic back outside so it never reaches its target.¹³ During reproduction, these new traits are ('vertically') passed on to the offspring.¹

Acquired resistance through horizontal gene transfer

Resistance to antibiotics may also be acquired through the exchange of mobile genetic elements across two bacteria of the same generation; this is called 'horizontal gene transfer' (HGT). This path of resistance acquisition is particularly worrisome as it can happen between different bacterial strains or between different species and in nearly all matrices (e.g. soil, water, gut or food).¹⁴



The transfer of antibiotic resistance through HGT is most often realised through plasmids, i.e. pieces of DNA which are transferred between bacterial cells.¹⁵ Another mechanism for passing resistance traits between bacteria is through viruses. The resistance traits from one bacterium are first packed in the head portion of the virus and subsequently injected into any new bacteria it attacks. Bacteria also have the ability to acquire naked, “free” DNA from their environment.¹⁵

Some families of antibiotics have a higher likelihood to induce resistance in bacteria, and some bacteria are more prone to develop resistance against antibiotics. For instance, resistance to quinolones appeared as soon as they were introduced into clinical medicine, through mutations and plasmid exchanges.¹⁶ While the use of fluoroquinolones in the United States increased by ~40% in the 1990's, the rate of resistance to ciprofloxacin doubled among gram-negative bacilli in intensive care units.¹⁶ With regard to bacteria, *Staphylococcus aureus* for instance has been able to develop efficient mechanisms to neutralize new antibiotics as rapidly as they were introduced.¹⁷ The rise of methicillin-resistant *S. aureus* (MRSA) is a serious problem worldwide, as MRSA strains have emerged with concomitant resistance to many commonly used antibiotics (aminoglycosides, macrolides, fluoroquinolones, chloramphenicol, and tetracycline, see multidrug-resistance in section 2.1.4).¹⁷

The susceptibility of bacteria to antibiotics is assessed by in vitro tests, called antimicrobial susceptibility testing. These tests allow to classify the bacteria into the categories **susceptible**, **intermediate**, or **resistant** to the antibiotic tested, according to specific criteria (in addition to quantitative values).^d **Non-susceptibility** to a specific antibiotic refers to a bacterium that is either intermediate or (fully) resistant. A bacterial isolate is considered resistant to

an antimicrobial category when it is non-susceptible to at least one agent in that category.¹⁸

Last but not least, it is important to mention that **bacteria become antibiotic-resistant, not humans or animals**.

2.1.3 How does antibiotic resistance spread?

Poor hygiene, poor sanitation, poor infection control practices, inadequate sanitary conditions and inappropriate food-handling all encourage the spread of bacteria, hence antimicrobial resistance.¹⁹ Bacteria are found in people, animals, food, and the environment (in water, soil and air). As any other bacteria, resistant bacteria can spread from person to person, between people and animals, including from food of animal origin or via environmental surfaces and waterways.²⁰

International traveling and trade help spread resistant bacteria around the globe. Animals for food production are transported across borders just like fruit and vegetables, and the bacteria follow along. This contributes to the complexity of the antibiotic resistance problem and underpins once more the fact that it is a global question.¹⁹

2.1.4 Multidrug resistant organisms

Any bacterium that acquires resistance genes, whether by spontaneous mutation or by genetic exchange with other bacteria (Box 2), has the ability to resist to one or more antibiotics. Because bacteria can collect multiple resistance traits over time, they can become **resistant to different families of antibiotics**. This is called multidrug-resistance (MDR) and is particularly problematic as it may severely limit the available treatment alternatives for that infection.¹¹ In general, when bacteria develop resistance to one drug, it is more likely to develop resistance against one or more other drugs.²¹ This

^d The susceptibility of a bacterial strain to an antimicrobial agent is analysed by in vitro determination of the minimal inhibitory concentration (MIC), which is the lowest concentration of an antimicrobial drug that inhibits the visible growth. To classify the tested strain as susceptible, intermediate or resistant, MIC values are compared with thresholds or cut-off values. In Europe, the

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints (or quantitative criteria) are recommended for use, but many laboratories used (and are maybe still using) the US based CLSI (Clinical & Laboratory Standards Institute) breakpoints. The method used has an influence on the test result in terms of category.



has been observed with different bacteria, yet the underlying mechanisms are still not fully understood.

The World Health Organization (WHO) reports that the bulk of the MDR burden is caused by a relatively limited number of organisms, which includes *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Staphylococcus aureus* (*S. aureus*), *Streptococcus pneumoniae* (*S. pneumoniae*), Nontyphoidal *Salmonella*, *Shigella*, *Neisseria gonorrhoeae*, *Mycobacterium tuberculosis* and *Plasmodium malariae*^{e,23}

In 2011, the European Centre for Disease Prevention and Control (ECDC) and the US Centers for Disease Control and Prevention (CDC) jointly published a standardized international terminology to describe acquired resistance profiles in *Staphylococcus aureus*, *Enterococcus* spp., *Enterobacteriaceae* (other than *Salmonella* and *Shigella*), *Pseudomonas aeruginosa* and *Acinetobacter* spp., all bacteria often causative of healthcare-associated infections and prone to multidrug resistance.¹⁸

2.1.5 Resistance in community and healthcare acquired infections

Although the bulk of antibiotics is prescribed in the ambulatory sector, the hospital environment favours the emergence and spread of resistant bacteria.⁹ The proportion of patients exposed to antibiotic treatment is also higher in hospitals.²⁴ Healthcare acquired infections (HAI), also known as nosocomial infections, usually show higher levels of antibiotic resistance, including multidrug resistance, compared to community acquired infections, as this is the case for MRSA.²⁵ A number of multidrug resistant healthcare acquired infections represent today one of the high public health threats. An example is the extended-spectrum beta-lactamase producing *E. coli* strains that have been responsible for outbreaks in Belgian hospitals.^{26, 27} Infection control measures are designed to prevent the spread of pathogens in

healthcare facilities, including those with AMR,¹ but they were considered out of scope for this study that focused on the prudent use of antibiotics.

Recently the rise and spread of multidrug resistance has also been observed among community-acquired infections,²⁸ including in our country.^{29, 30}

2.2 What is prudent antibiotic use?

The concept of prudent (or rational) use of medicines dates from the eighties. It is defined in EU guidelines as the use which benefits the patient while at the same time minimises the probability of adverse effects (including toxicity and the selection of pathogenic organisms, like *Clostridium difficile*) and the emergence or spread of antimicrobial resistance. Other terms that have been used with the same purpose include judicious, rational, adequate, correct and optimal.³ The WHO also specifies that it requires that patients receive medication appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time.^{31, 32}

There are at least two additional factors that need to be considered in relation to the **prudent use of antibiotics**:⁹

- For an antibiotic to be effective, it must be of good quality, and the bacteria causing the infection need to be susceptible to it. The prudent use of antibiotics therefore requires information derived from microbiological susceptibility testing and assured quality of the antibiotic being used.
- The use of antibiotics has consequences for both the individual patient and for society. Individual use can lead to selection of antibiotic-resistant bacteria which may then infect other members of the population, causing infections that may be difficult to treat. Antimicrobials are the only class of today's medicines for which obsolescence results from use.

^e In 2017, WHO complemented this list of microorganisms with a list of 12 antibiotic-bacterium combinations for which there is an urgent need to produce new antibiotics due to the high AMR rates and limited new therapeutic options in the research & development pipeline.²²



Unfortunately, for the first factor, diagnostic and susceptibility information are not available at the time of prescription; the second is often ignored because the perceived benefit to an individual patient is considered to outweigh the long-term impact on society (cf. *infra*).⁹

Non-prudent prescription of antibiotics includes over-prescription, under-prescription, prescription of unnecessary antibiotics or antibiotic combinations, inappropriate dosage, inappropriate duration of treatment. Healthcare professionals may prescribe too many drugs or inappropriate drugs because of fear of treatment failure, uncertainty about the cause of the infection, lack of knowledge of the local antibacterial resistance situation, real or perceived patients' expectations, drug company promotional efforts, or for personal financial gain. Consumers may practice self-medication using unnecessary or ineffective antibiotics, or insufficient quantities of an appropriate antibiotic.⁹

The prescription of antibiotics is influenced by a complex interplay between the knowledge, attitude, and behaviour of the prescriber and the patient,³³ as well as other factors that are described in Chapter 5. The interventions to facilitate the prudent prescribing of antibiotics are further elaborated in Chapter 6.

2.3 Use and misuse of antibiotics

As said earlier, the development of antibacterial resistance is **accelerated by the use or misuse of antibiotics in humans and animals**. Antibiotics have been extensively misused in both humans and (food-producing) animals in ways that favour the selection and spread of resistant bacteria. Examples are the use of antibiotics to treat conditions that are not caused by a bacterial infection, inappropriate choice of antibiotics, inadequate dosing, inadequate duration of therapy, poor adherence to treatment, substandard drugs, and the use of antibiotics as growth promoters in animals (see Box 3).^{9, 20, 34} One of the main strategies to contain AMR is therefore to increase prudent use and to reduce misuse of antibiotics.

Box 3 – Examples of non-prudent use of antibiotics

A frequent example of misuse in ambulatory care is the prescription of **antibiotics for upper respiratory tract infections**, which are in the majority of cases caused by viruses. A retrospective observational study of primary care databases revealed that in Belgium, more than 60% of patients with bronchitis, tonsillitis, sinusitis or otitis media were prescribed an antibiotic; and for none of these diagnoses the patients were prescribed the first choice antibiotic (as recommended by the European consensus).³⁵

Perioperative surgical prophylaxis (PAP) is recognised as a valuable tool to reduce post-operative surgical site infections, but it should cover the peri-operative period only and a single dose is advised for most cases (unless there is extensive blood loss or the procedure is prolonged).^{36, 37} Its prolongation beyond this time period offers no additional benefit with respect to the prevention of surgical site infections. Yet, prolonged PAP is a driver for the development of bacterial resistance.³⁸ Nevertheless, the 2016-2017 ECDC point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals (see section 4.2.1) revealed that 54.2% of antimicrobials for surgical prophylaxis were prescribed for more than 1 day.³⁹

2.4 The burden of antibacterial resistance

Today antibacterial resistance is one of the biggest threats to global health, food security and development; it is rising to dangerously high levels in all parts of the world.²⁰ New resistance mechanisms are emerging and spreading globally, making it harder and sometimes impossible to treat common infectious diseases, like pneumonia, tuberculosis, blood poisoning, gonorrhoea, and foodborne diseases because antibiotics become less effective.

Patients infected by antimicrobial-resistant microorganisms are significantly more likely to develop complications (e.g. +13% limb loss and +71% complications in the central nervous system for infections by methicillin resistant *S. Aureus*) and to die (e.g. up to 2-3 times higher mortality depending on the microorganism).¹ Infections caused by antimicrobial-resistant pathogens may also require more intensive and prolonged



treatments with second line therapies. In some cases, these antimicrobial therapies may cause more adverse reactions or may have toxic secondary effects.^{1, 40} Based on 2015 European Antimicrobial Resistance Surveillance Network (EARS-Net) data^f, it was estimated that in countries of the EU and European Economic Area (EEA) there were 671 689 infections (95% Uncertainty Interval (UI) 583 148-763 966) with antibiotic-resistant bacteria and that these infections caused 874 541 (95% UI 768 837-989 068) disability-adjusted life years (DALYs, see Box 4) and 33 110 (95% UI 28 480-38 430) deaths in 2015.⁴¹

Box 4 – Disability-adjusted life years

The metric disability-adjusted life year(s) (DALY) is an internationally recognized summary measure of population health; it quantifies the burden of a disease as the number of healthy years of life lost to morbidity and mortality. It facilitates comparing the relative impact of diseases and risk factors over time.⁴² DALYs for a disease or health condition are calculated as the sum of the Years of Life Lost (YLL) due to premature mortality in the population and the Years Lost due to Disability (YLD) for people living with the health condition or its consequences.

Recently, the OECD developed a micro-simulation model to produce comparable cross-country estimates of the health and economic impact of AMR for the period 2015-2050, for a comprehensive set of infections susceptible to develop resistance^{9, 43}. Individual analyses were performed for 33 OECD and European Union/European Economic Area (EU/EEA) member countries; no EU/EEA average was provided (Table 10).

The OECD model estimates that on average AMR causes per year around 33 000 deaths in the EU/EEA countries; of these around 533 occur in Belgium. With an average of 4.65 deaths per 100 000 persons due to AMR each year, Belgium ranks 14th (highest). In terms of burden of disease, the model further estimates for Belgium that each year AMR results in 114.09 DALYs lost per 100 000 persons (or 13 149 DALYs for the whole population), which situates Belgium right in the middle across all included countries. With an average of 664.3 extra hospital days associated with AMR per 100 000 citizens per year (or 76 586 extra hospital days for the whole population), Belgium ranks 11th (highest). Just like in the other countries, more than 60% of the extra hospital days occur in citizens of at least 50 years old, while one fifth occurs in children under 10 years of age. Last but not least, the simulation estimates that AMR will cost the Belgian health system around USD Purchasing power parity 27 727 390 every year.⁴³

^f The incidence of infections with 16 antibiotic resistance-bacterium combinations was estimated from European Antimicrobial Resistance Surveillance Network (EARS-Net) January-December 2015 data that were country-corrected for population coverage.

⁹ The model accounts for 8 bacteria and a total of 17 antibiotic-bacterium combinations and simulates resistant and susceptible infections occurring in five body sites: bloodstream, respiratory system, urinary tract, surgical site, and other. Data to model the epidemiology of infections in the EU/EEA were made available by the ECDC.⁴³

**Table 1 – Burden of AMR on population health – estimates for 2015-2050**

	Belgium	EU/EEA minimum	EU/EEA maximum
Average annual AMR mortality rate per 100 000 persons	4.65	0.28 (Iceland)	18.17 (Italy)
Cumulative number of AMR deaths over 35 years	22 564	40 (Iceland)	456 486 (Italy)
Average annual number of DALYs per 100 000 persons, attributable to AMR	114.09	7.07 (Iceland)	489.15 (Italy)
Average annual number of extra hospital days associated with AMR	664.3	42.9 (Iceland)	2304.2 (Italy)
0-9 years (%)	141.9 (21%)	9.2 (21%)	492.2 (21%)
10-49 years (%)	96.7 (15%)	6.2 (14%)	335.4 (15%)
50-69 years (%)	178.2 (27%)	11.5 (27%)	618.1 (27%)
≥ 70 years (%)	247.5 (37%)	16.0 (37%)	858.5 (37%)
Annual health care expenditure associated with AMR ^{\$}	240 397.07	4364.29 (Iceland)	662 584.16 (Italy)

\$: expressed as USD Purchasing power parity (PPP^h); no EU/EEA (population-weighted) mean/median values available from the publication, hence minimum/maximum (i.e. EU/EEA country with lowest c.q. highest result) provided to situate Belgian data.

Source: Stemming the Superbug Tide - Just a few dollars more, OECD, 2018⁴³

2.5 Time for action

Recognizing the public health crisis due to AMR, several nations, international agencies, and many other organizations worldwide have taken action to counteract it through strategies applied in the relevant sectors.

For instance, the **World Health Assembly** has established the **rational use of antibiotics** as a **priority** in its 2005 assembly, which urged member states to enhance rational use of antimicrobial agents.⁴⁴ Other global efforts include the 2016 United Nations Political Declaration on AMR and the 2015 **WHO Global Action Plan on AMR**, which was subsequently adopted by the World Animal Health Organisation (OIE) and the Food and Agriculture Organization (FAO).² AMR has also been addressed in the G7 and G20 forums.¹

Also at the European level, the evolving AMR problem was recognised. In 1998, the Chief Medical Officers of the EU Member States organised the first major conference on AMR, which resulted in the Copenhagen Recommendations.⁴⁵ In June 2017, the **European Commission** published a new **European one health action plan** against antimicrobial resistance (AMR) with concrete actions that the European Commission will develop and strengthen as appropriate for a more integrated, comprehensive and effective approach to combating AMR.⁴⁶

^h The purchasing power of a currency refers to the quantity of the currency needed to purchase a given unit of a good, or common basket of goods and services. Purchasing power is clearly determined by the relative cost of living and inflation rates in different countries. Purchasing power parity means equalising the purchasing power of two currencies by taking into account these cost of living and inflation differences. (<https://www.economicsonline.co.uk/>)

**Key messages**

- Antimicrobial (antibacterial) resistance (AMR/ABR) is a natural phenomenon. Yet, its development is accelerated by the selection pressure exerted by the use or misuse of antimicrobials/antibiotics in humans and animals. Poor infection prevention and control practices and inadequate sanitary conditions favour the further spread of these resistant microbes/bacteria.
- According to WHO, the prudent use of medicines requires that patients receive medication appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.
- Today antibacterial resistance is one of the biggest threats to global health, food security and development. The OECD estimated the annual health and economic impact of AMR for the period 2015-2050 for Belgium: around 533 deaths, an average of 114.09 DALYs lost per 100 000 citizens, an average of 664.3 extra hospital days and around USD Purchasing power parity 240 397.07.
- Recognizing the public health crisis due to AMR, several nations, international agencies, and many other organizations worldwide have taken action to counteract it through strategies applied in the relevant sectors.

3 ANTIBIOTICS IN BELGIUM

3.1 Who can prescribe antibiotics in Belgium?

3.1.1 Human sector

The main prescribers of antibiotics in human medicine in Belgium are physicians and dentists. Since 2016 midwives are also allowed to prescribe some medicines autonomously, but with regard to antibiotics this is limited to intrapartum antibiotic prophylaxis with Penicillin G or Amoxicillin in group B streptococcus (GBS) colonized women.⁴⁷

The choice of the antibiotic, as well as the posology and the duration of intake, belong to the therapeutic freedom of the prescriber. Yet, in an advice of the National Council of the Order of Medical Doctors (dd. 20 January 1996) it was stated that in case of conflicting interests between Article 36 of the Code of Medical Duties (i.e. the diagnostic and therapeutic freedom of a physician) and Article 34 (i.e. a physician must act according to current scientific knowledge), Article 36 remains subordinate to Article 34.⁴⁸ By consequence therapeutic freedom is subordinate to the obligation to act according to scientific knowledge.

In a later advice (dd. 6 March 2010), the National Council of the Order of Medical Doctors further stipulated that in case a prescribing physician does not respect the formulary and the therapeutic recommendations developed by the hospital antibiotic stewardshipⁱ group, despite the direct action of the antibiotic stewardship group's deputy in the hospital antibiotic management team (see Box 25 in section 6.1.1.2), the chief medical officer and the medical board have to ensure that this behaviour does not harm the quality of care nor public health.⁴⁹

ⁱ Antibiotic stewardship refers to a set of coordinated strategies to improve the prudent use of antibiotics with the goal of enhancing patient health outcomes, reducing resistance to antibiotics, and decreasing unnecessary costs. For more information the reader is referred to Box 24 in section 6.1.1.2.



3.1.2 Veterinary sector

As specified in the Belgian law on the practice of veterinary medicine, veterinarians are the only professionals who have the authority to prescribe medicines (among which antibiotics) for veterinary use.⁵⁰

In contrast to the human sector, veterinarians are also allowed to deliver the medication they prescribe. This particular situation may lead to a conflict of interest since veterinarians do not only take care of animals' health (by means of prevention, diagnosis, treatment and counselling), but they also earn part of their income through the sale of medication. In 2010 a survey among 65 Belgian veterinarians working mostly with pigs showed that selling veterinary medicines is an important proportion of the veterinarian's income (43%).⁵¹

Pharmaceutical companies are not allowed to sell antimicrobials directly to veterinarians; a wholesaler-distributor acts as intermediary. Volume price incentives (a greater discount for bigger purchases) are not allowed, but non-volume related discounts can be given by the wholesalers-distributors.⁵⁰

Key messages

- **The main prescribers of antibiotics in human medicine in Belgium are physicians and dentists.**
- **Unlike physicians and dentists, veterinarians are also allowed to deliver the medication they prescribe. This particular situation may lead to a conflict of interest.**

3.2 Who can obtain antibiotics in Belgium and how?

3.2.1 Human sector

In line with the European Union Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine,⁵² Belgian legislation prevents the sale of antibiotics (and other antimicrobials) for systemic use 'over-the-counter', i.e. without a prescription. Some antibiotics for dermatological, ophthalmological, nasal or oropharyngeal use can be purchased 'over-the-counter' (e.g. Fucidic acid for dermatological and ophthalmological use, Framycetin nasal spray).

In the latest Eurobarometer survey on public use of and knowledge about antibiotics (see Box 5) 95% of the Belgian participants reported that they obtained the last course of antibiotics they used from a medical practitioner. A minority (5%) stated they used antibiotics without a prescription or used those left over from a previous course.⁵³

Box 5 – Eurobarometer survey on public use of and knowledge about antibiotics

Since 2009, the Directorate-General for Health and Consumers (European Commission) has monitored the levels of public use of and knowledge about antibiotics through three EU wide surveys in 2009, in 2013 and in 2016.⁵³ During the last survey, carried out in April 2016, a representative sample of 27 969 respondents aged 15 years and over from different social and demographic groups was interviewed face-to-face at home in their mother tongue; in Belgium 1 007 people were interviewed by TNS Dimarso.⁵³

Last but not least, in the battle against antimicrobial resistance, it must be realised that the internet provides opportunities for non-prescription sales of antibiotics on an unprecedented scale. Consumers anywhere in the world are now only a few clicks away from online pharmacies, some of which are willing to ship antibiotics anywhere in the world without prescription.⁵⁴



3.2.2 *Who can administer antibiotics to animals and who is allowed to keep stocks of medicines at farms?*

The treatment of animals with medicines is only possible after a veterinarian's intervention. The veterinarian diagnoses and starts treatment. The veterinarian can decide to delegate the follow-up treatment to the farmer and delivers then the necessary medicines to do so. The volume of the medicine should be function of what is needed for the follow-up treatment.

To do the follow-up treatment farmers are allowed to keep stocks of medicinal products at their farm, which is described in several Royal Decrees.⁵⁵⁻⁵⁷ The volume of medicines present at the farm should not exceed what is necessary for the prescribed treatment, with a maximum of two months for farmers with a guidance contract^j,⁵⁵ and limited to three weeks for farmers without.⁵⁷ In theory, left-overs can only be used on indication of a veterinarian, hence a new administration and provision document ('toedienings- en verschaffingsdocument' (TVD) – 'document d'administration et de fourniture' (DAF)) is needed.

Antibiotics can also be added to animal feed^k. Medicated feed is a mix of feed and one or more medicated premixes. The premixes are added to the feed and as such sold to farmers for their therapeutic and prophylactic characteristics. In case the veterinarian sees the need for the addition of medicines (e.g. antibiotics for therapeutic reasons) to animal feed, he can prescribe the medicated feed for a maximum follow-up treatment of one month within a guidance contract. Without such a contract the duration is limited to 15 days.⁵⁶

Key messages

- **Belgian legislation prevents the sale of antibiotics (and other antimicrobials) for systemic use 'over-the-counter', i.e. without a prescription. Some antibiotics for dermatological, ophthalmological, nasal or oropharyngeal use can be purchased 'over-the-counter'.**
- **In the 2016 Eurobarometer survey, only a minority (5%) of Belgian interviewees reported self-medication with antibiotics (without a prescription).**
- **A veterinarian can delegate the follow-up treatment to the farmer and delivers then the necessary medicines to do so. In the legislation the maximal volume of this medicine stock left at the farm is clearly stipulated.**
- **Upon prescription by the veterinarian, medicines (and thus also antibiotics) can also be added to animal feed. The maximum length of the use of medicated feed is also defined in the legislation.**

^j A guidance contract further implies that the veterinarian has to visit the farm at least six times per year with a maximum interval of two months between two visits. The veterinarian is responsible for providing information, advice, supervision, assessing the animals' health status, preventing and treating diseases.⁵⁷

^k Almost exclusively for pig farming.



3.3 Financial aspects

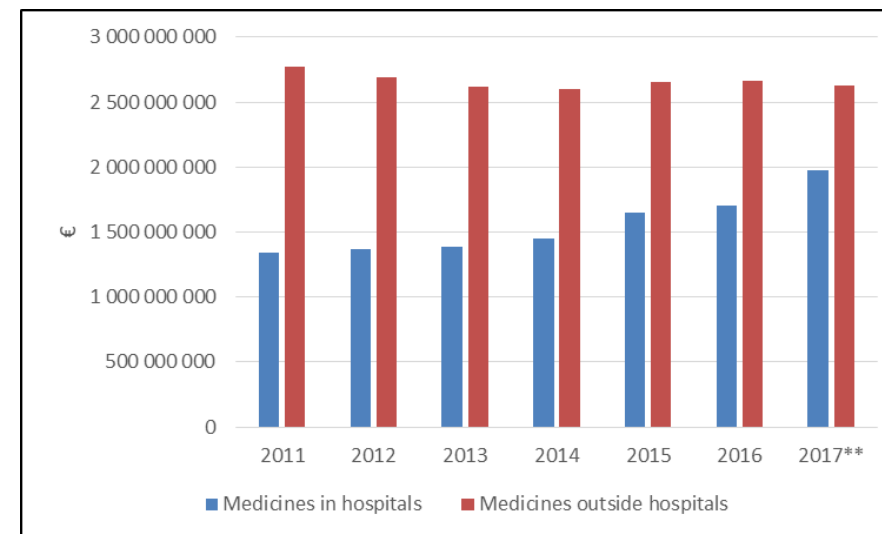
3.3.1 Human sector

3.3.1.1 Expenses for antibiotics

Note: In this section the financial burden of antibiotics from the perspective of the health insurance as well as from the patient's perspective is described, based on the most recent available data. Trends are described, without exploring the underlying causes, as this was considered out of scope for this project. How the patient's share is determined (based on reimbursement categories) is explained in the following section.

In 2016¹, the total health insurance expense for **all reimbursed medicines** used in the ambulatory and hospital sector was € 4 372 million and the total patients' share was € 464 million. Over the 2011-2017 period, the total health insurance expense for all reimbursed medicines used in the ambulatory sector fluctuated between € 2 605 million and € 2 773 million, while in the hospital sector it gradually increased from € 1 341 million to € 1 978 million (Figure 1). During this period, the total health insurance expense for all medicines used in both sectors ranged between € 988 and € 1 114 per 1000 inhabitants per day. In the same time span, the total patients' share for reimbursed medicines ranged between € 113 and € 134 per 1000 inhabitants per day. It is important to note that patients' expenses for medicines for which there is no reimbursement (e.g. paracetamol) are not included in these data.

Figure 1 – Total health insurance expense for all medicines, 2011-2017**



** The 2017 data are extrapolations based on available accounting data

Source: RIZIV - INAMI

Over the 2011-2017 period, the total health insurance expense for antibiotics decreased from nearly € 77 million to € 65 million in the hospital sector and from about € 120 million to € 80 million in the ambulatory sector (Figure 2). During this period, the total health insurance expense for all antibiotics used in both sectors decreased from € 49 to € 35 per 1000 inhabitants per day (Figure 3). When the health insurance expenses for antibiotics are split up by ATC 4 class (see Box 6), it is clear that the biggest part is spent on beta-lactam antibacterials and penicillins (J01C), followed by the quinolones (J01M), the other beta-lactam antibacterials (J01D) and the macrolides, lincosamides and streptogramins (J01F).

¹ At the moment this report is written the most recent complete data are these of 2016; the 2017 data presented in this section are extrapolations based on available accounting data.



Box 6 – Anatomical Therapeutic Chemical (ATC) Classification

The Anatomical Therapeutic Chemical (ATC) Classification System is used for the classification of active substances of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Drugs are classified in groups at five different levels:

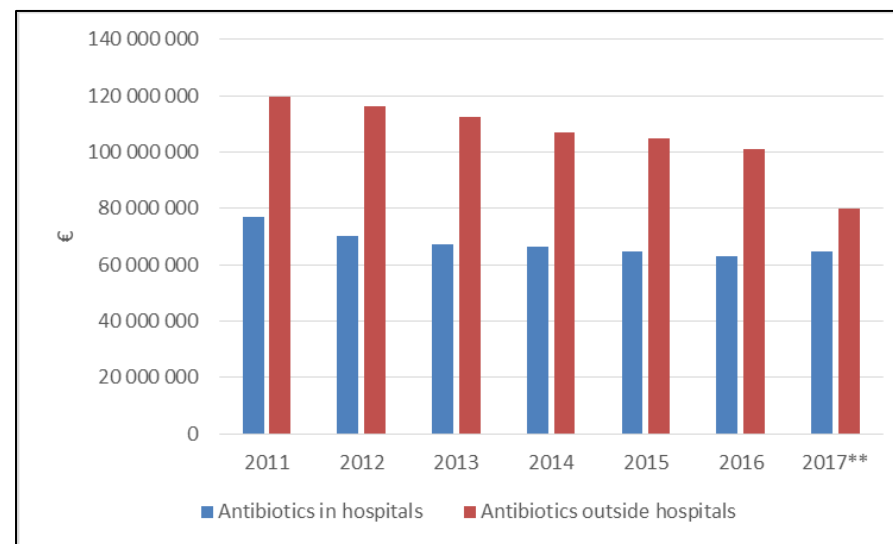
- ATC 1st level: The system has fourteen main anatomical or pharmacological groups
- ATC 2nd level: Pharmacological or Therapeutic subgroup
- ATC 3rd & 4th levels: Chemical, Pharmacological or Therapeutic subgroup
- ATC 5th level: Chemical substance

A medicinal substance can be given more than one ATC code if it is available in two or more strengths or routes of administration with clearly different therapeutic uses.

Antibacterial products for systemic use are classified in ATC group J01.

Source: http://www.who.int/medicines/regulation/medicines-safety/toolkit_atc/en/⁵⁸

Figure 2 – Total health insurance expense for antibiotics, 2011-2017**



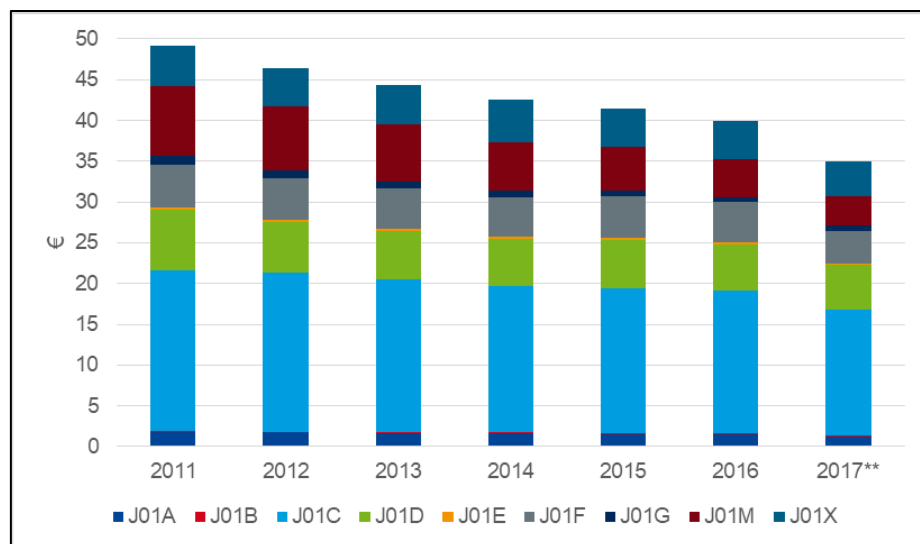
** The 2017 data are extrapolations based on available accounting data

Source: RIZIV – INAMI

Over the same period, the total patients' share for antibiotics used in the hospital sector ranged between € 0.5 and 0.6 million. For antibiotics used in the ambulatory sector a decrease in the patients' share is observed from € 34 million in 2011 to € 23 million in 2016, followed by a sudden rise to € 37 million in 2017. The latter may (in part) be explained by the change in reimbursement category for all antibiotics used in the ambulatory sector resulting in an increased patients' share (cf. infra).



Figure 3 – Evolution of the health insurance expense for antibiotics per 1000 inhabitants per day by ATC 4 class, 2011-2017**



ATC4 codes: J01A: Tetracyclines, J01B Amphenicols, J01C: Penicillins, J01D: Other beta-lactam antibacterials, J01E: Sulfonamides and trimethoprim, J01F: Macrolides, lincosamides and streptogramins, J01G: Aminoglycoside antibacterials, J01M: Quinolone antibacterials, J01X: Other antibacterials; **: The 2017 data are extrapolations based on available accounting data
Source: RIZIV – INAMI

For the health insurance, the expense for antibiotics represented in 2011 5% of the total expense for reimbursed medicines and decreased to 3% in 2017. For the patients, the expense for antibiotics represented in 2011 7% of the total medicine expense, decreased to 5% in 2016 and increased again to 8% in 2017.

3.3.1.2 Patients' share in antibiotics

In Belgium drugs are classified in 7 reimbursement categories. The reimbursement category of a pharmaceutical specialty depends on its **medical therapeutic interest** and the **'necessary' character of the specialty**. The category indicates the extent to which the health insurance provides reimbursement and thus the patients' share.⁵⁹

The amount of money a patient pays for the antibiotics he takes, **depends on the context**.

- In the *ambulatory setting* (i.e. outside the hospital) the patient's share has increased since 1 May 2017 to 88.39% (in case the ex-factory price (i.e. price paid by the wholesaler to the pharmaceutical firm) is lower than € 14.38) or € 5 + 54% (in case the ex-factory price is higher than € 14.38, Table 2) as antibiotics were then moved from category B to category C (cf. infra).⁵⁹
- When a patient is admitted in hospital for *day care* (i.e. he is admitted and discharged on the same day), the patient's share for antibiotics is 25%, thus lower than for ambulatory patients (see Table 2, last column).
- In case of *hospitalisation* in an acute hospital, patients have to pay for reimbursed medicines (among which antibiotics) a fixed co-payment of € 0.62 per day in hospital, irrespective of the drug reimbursement category and irrespective of the number of drugs actually consumed (cf. infra).⁵⁹

Table 2 – Drug reimbursement categories B and C and patients' share in 2018

Category	Description	Patients' share - Ambulatory patients		Patients' share - Day care ^s
		if ex-factory price < € 14.38	if ex-factory price ≥ € 14.38	
Category B	Therapeutically important pharmaceutical specialties	44.20% (26.52%*)	€ 2.5 + 27.00% (€ 1.5 + 16%*)	25% (15%*)
Category C	Drugs intended for symptomatic treatment	88.39%	€ 5 + 54%	50%

*Ex-factory price: price paid by the wholesaler to the pharmaceutical firm; *: patients' share for inhabitants with a low income who are entitled an increased reimbursement; \$: day care: the patient is admitted and discharged on the same day*

Source: <http://www.riziv.fgov.be/> ⁵⁹ (last access: 8 August 2018)

3.3.1.3 Restrictive measures in the prescription, delivery and/or reimbursement of antibiotics

Over the years, the government has taken several measures to save on the budget for medicines and/or to improve their prudent use, leading to certain restrictions for prescribers and pharmacists (Box 7) and/or to a change in reimbursement. In the following paragraphs only measures with an impact on antibiotics are described. They are further discussed in section 6.1.

Ambulatory sector

The concept of 'cheapest medicine' applicable to antibiotics

Since May 2012 the concept of 'cheapest medicine' applies to all antibiotics sold outside the hospital. More precisely, pharmacists are obliged to deliver an **antibiotic** with the same active ingredient, the same way of administration, the same dose, the correct package size and specifications, but within the group of the '**cheapest medicines**', irrespective of the way the antibiotic is prescribed (by active ingredient or label).⁶⁰ In certain circumstances, the prescriber may request a medical objection to the selection of another commercial name by the pharmacist.

Box 7 – Examples of measures taken by the government to save on the budget for medicines

In 2005 the concept of **cheap medicines** ('Goedkope geneesmiddelen' – 'les médicaments bon marché') has been introduced: the government decided that physicians and dentists with a minimum prescription profile should **prescribe a minimum percentage of cheap medicines**.⁶¹ Pharmaceutical products that qualify as 'cheap medicine' are indicated as such in the medicine repertory, the respective websites (e.g. <http://www.bcfi.be/>) and the online tools. Anno 2018 the *minimum prescription profile* is defined as at least 200 packages for physicians and 30 for dentists during a period of 6 months. The *minimum percentage of cheap medicines* has been defined for each specialty and ranges anno 2018 between 38 and 91%. The measure is only relevant for medicines which are reimbursed and which are sold in pharmacies outside the hospital^m. In 2005, 2007, 2008, 2009, 2010 and 2015 and in February 2019 prescribers received individual feedback from RIZIV – INAMI so that they could adjust their prescribing behaviour when indicated.

^m For more detailed information the reader is referred to <http://www.riziv.fgov.be/nl/professionals/individuele Zorgverleners/artsen/verzorging/Paginas/goedkoop-voorschrijven-20150101.aspx#.WzXz5WAUmhc> -

<http://www.riziv.fgov.be/fr/professionnels/sante/medecins/soins/Pages/prescription-bon-marche-20150101.aspx#.WzX0X2AUmhc>



In May 2012 the concept of **cheapest medicines** ('goedkoopste geneesmiddelen' – 'les médicaments les moins chers') was launched: if on the prescription only the active ingredient (International Non-proprietary Name (INN), 'Voorschrift op Stofnaam' – 'Dénomination Commune Internationale') is specified, **the pharmacist has to deliver** a medicine with the same active ingredient, the same way of administration, the same dose, the correct package size and specifications, but within the **group of the 'cheapest medicines'**.⁶⁰ This rule also applies to all antibiotics and all antifungal agents, irrespective of the way they are prescribed (by active ingredient or label).⁶⁰ Again, this measure is only applicable to medicines sold outside the hospitalⁿ.

Source: <http://www.riziv.fgov.be/>

Antibiotics delivered by pharmacies open to the public moved from category B to category C

Until April 2017, antibiotics delivered by pharmacies open to the 'general public' (as opposed to e.g. hospital pharmacies) were classified into category B, this is the reimbursement category for therapeutically important pharmaceutical specialties (which includes among others drugs involved in the treatment of Parkinson disease, hypertension and asthma, see Table 2).

Since **1 May 2017, antibiotics intended for per os (i.e. oral) administration and delivered by pharmacies open to the public have moved from category B to category C**, this is the reimbursement category for drugs intended for symptomatic treatment. This category includes among others drugs involved in ophthalmology and mucus-thinning agents for the treatment of chronic bronchitis. As is presented in Table 2, this measure has increased the patient's share for these antibiotics. The measure has been taken within the frame of an austerity measure, the rationale being that the overuse of antibiotics should be tackled in order to restrain the antibacterial resistance that results from it.⁶² For patients admitted in hospital for an inpatient stay (i.e. a patient admitted into a hospital who is not discharged on the day of admission) this measure has no impact.

Quinolones included in 'Chapter IV' of the list of reimbursable medicines

From 1 May 2018 onwards, quinolones for per os administration and delivered by pharmacies open to the public have been included in 'Chapter IV' of the list of reimbursable medicines ('Hoofdstuk IV van de lijst van de vergoedbare farmaceutische specialiteiten' – 'Chapitre IV de la liste des spécialités pharmaceutiques remboursables') (Box 8).

Box 8 – Chapter IV of the list of reimbursable medicines

The **reimbursement** of drugs listed in Chapter IV is **subject to conditions** that are imposed for medical and/or budgetary reasons. This means that the reimbursement is limited e.g. in terms of indications, target group or age group. In addition, a prior authorization from the advisory physician must be requested for these pharmaceutical specialties.⁶³

ⁿ For more detailed information the reader is referred to <http://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziektenfonds/geneesmiddel-gezondheidsproduct/geneesmiddel-voorschrijven/Paginas/goedkoopste->

<http://www.riziv.fgov.be/fr/themes/cout-remboursement/par-mutualite/medicament-produits-sante/prescrire-medicaments/Pages/medicaments-moins-chers.aspx#.WzYO0CCxVPY>



The purpose of including the quinolones in Chapter IV is to counter the overuse of antibiotics in Belgium and the development of resistance that results from this by limiting the inadequate use of certain antibiotics.⁶⁴ The change in the reimbursement conditions applies to the (fluoro)quinolones which contain as active ingredient ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin or ofloxacin.⁶⁴ For these specific antibiotics, **reimbursement is limited to the following infections or circumstances:**⁶⁴

- Acute pyelonephritis, after taking a culture for an antibiogram
- Acute prostatitis
- Chronic prostatitis, after taking a culture for an antibiogram
- Acute urethritis, after taking a culture for an antibiogram
- Orchi-epididymitis
- Pelvic Inflammatory Diseases
- Uncomplicated acute diverticulitis
- In patients with a severe co-morbidity, with a malignancy or HIV infection or treated with an immunosuppressant
- An exceptional and urgent situation that requires starting treatment with a quinolone

Since antibiotics are administered in acute situations prior authorization from the advisory physician is not feasible. Therefore in the case of the quinolones verification of the conditions is done a posteriori: the prescriber has to keep the elements which illustrate that all reimbursement conditions have been

fulfilled in the patient's medical file, at the disposal of the health insurance advisor.⁶⁴

Hospital sector

As several studies^o indicated that peri-operative antibiotics were not prescribed according to the guidelines,^{65, 66} a change in the reimbursement system has been introduced in May 1997. Until then, the costs of antibiotics administered in Belgian hospitals were nearly fully reimbursed by the health insurance.⁶⁷

From May 1997 onwards, a fixed lump-sum for antibiotic prophylaxis was added to the fee for the surgical procedure. This lump-sum was based on (inter)national guidelines describing the indication for the prophylaxis, the choice of product, the dose and duration. The lump-sum covered 75% of the cost for antimicrobial prophylaxis as described in the guidelines. In addition, only 25% of the actual administered antimicrobial prophylaxis was reimbursed. If the surgeon thus prescribed peri-operative antibiotics according to the guidelines, 100% of the expenses was covered. If he preferred to choose a more expensive antibiotic or if he administered peri-operative antibiotics during a prolonged time, only partial reimbursement was provided to the hospital. The fact that 25% of the reimbursement was based on the actual antibiotic used, was intended for monitoring purposes. In this way an overview of the actually used antibiotics is possible.

Since 1 July 2006 this reimbursement system has been replaced by a new financing mechanism for most drugs used in hospitals: medicines administered during inpatient stays (i.e. when the patient stays at least one night in hospital), are financed through a prospective budget.⁶⁸ This budget is based on the hospital's case-mix and the national average of the drugs' use per APR-DRG (All Patient Refined Diagnosis Related Group) and severity of illness (SOI)^p; it is calculated once a year by RIZIV – INAMI. Each

^o In the study by Kurz et al. (1996) for instance it was illustrated that peri-operative prophylaxis was given in 57% of the procedures for which prophylaxis is generally not recommended, while it was not used in 14% of the procedures for which it is generally recommended. Moreover, prophylaxis was prolonged by more than 2 days postoperatively after 23% of the procedures and by more than 4 days in 8%.⁶⁵

^p The APR-DRG system is a type of patient classification system that aims to define medically coherent and cost homogeneous groups. APR-DRGs extend the basic DRG structure by adding two sets of subclasses to each base APR-DRG, i.e. severity of illness (SOI) and risk of mortality (ROM). Within each APR-DRG there are four grades of SOI: 1 = minor; 2 = moderate; 3 = major;



year, the hospitals are notified what their global medicines' budget is and the lump sum they can bill to the patients' health insurance for medicines.

Medicines (among which all antibiotics (ATC J01)) are included in this lump sum for approximately 75% of their value. The remaining 25% is reimbursed per product. Yet, some medicines are not included in this budget (e.g. retroviral drugs, antineoplastic drugs, orphan drugs, but also some antifungal agents like caspofungin and voriconazole); they are reimbursed per product.

The prospective pharmaceutical budgeting for medicines administered during inpatient stays was intended to increase the rational use of drugs and to improve the control of expenses.⁷⁰ The evaluation of the impact of this measure is considered out of scope of this study.

3.3.2 Veterinary sector

Unlike the human sector, where there is (partial) reimbursement of costs of antibiotics, this is not the case for animal use. Antibiotics are fully paid by the owner of the animal taking antibiotics (both food-producing animals and pets).

Key messages

Over the years, the Belgian government has taken several measures to save on the budget for medicines and/or to improve their prudent use, leading to certain restrictions for prescribers and pharmacists and/or to a change in the reimbursement or payment system:

- **Since May 2012 the concept of 'cheapest medicine' applies to all antibiotics delivered by pharmacies open to the public: pharmacists are obliged to deliver an antibiotic with the same active ingredient, the same way of administration, the same dose, the correct package size and specifications, but within the**

group of the 'cheapest medicines', irrespective of the way the antibiotic is prescribed (by active ingredient or label).

- **Since 1 May 2017 antibiotics intended for per os (i.e. oral) administration and delivered by pharmacies open to the public have moved from category B to category C. The measure has been taken within the frame of an austerity measure; it has increased the patient's share for these antibiotics.**
- **Since 1 May 2018 quinolones for per os administration and delivered by pharmacies open to the public have been included in 'Chapter IV' of the list of reimbursable medicines, more precisely, their reimbursement is limited to certain infections or circumstances.**
- **Since 1 July 2006 there is a prospective pharmaceutical budgeting for most drugs, including antibiotics, administered during inpatient stays (i.e. when the patient stays at least one night in hospital); hence the payment system of a fixed lump-sum for antibiotic prophylaxis added to the fee for surgery (which was installed in May 1997) was then abandoned.**
- **In the veterinary sector, antibiotics are fully paid by the owner of the animal taking them.**

4 = extreme. Patients are allocated to an APR-DRG-SOI group on the basis of principal diagnosis, secondary diagnoses and procedures, age and sex of the patient and, for some APR-DRGs (e.g. burns), type of discharge.⁶⁹



3.4 Actors involved, inspired by the Viable Systems Model

3.4.1 Introduction

The description of the actors involved in the antibiotic policy field (e.g. prescription, use, training, coordination) in Belgium is inspired by the Viable Systems Model (VSM) as an organising principle (see Box 9). We used the VSM framework as a diagnostic tool and linked the functional elements to relevant actors in the field of human medicine to position actors in the field and identify gaps, i.e. functions that have not been taken up by any actor. Figure 4 presents the main actors involved in antibiotic prescription and use in the human sector, inspired by the Viable Systems Model (VSM). The same approach was used for the veterinary sector (see section 3.4.3).

Box 9 – The Viable Systems Model

The Viable Systems Model has been created by Stafford Beer to model any kind of organization.⁷¹ The framework is used to understand and (re)design organisations. It provides a model for the information flow required for learning and adaptation of an organisation in its wider environment,⁷² and it can be used as a diagnostic tool.⁷³ The VSM consists of three connected functional parts: the operational, the metasystem and the environment (Figure 4). Operation and metasystem are tightly coupled 'internal' elements embedded in an 'external' environment.⁷⁴

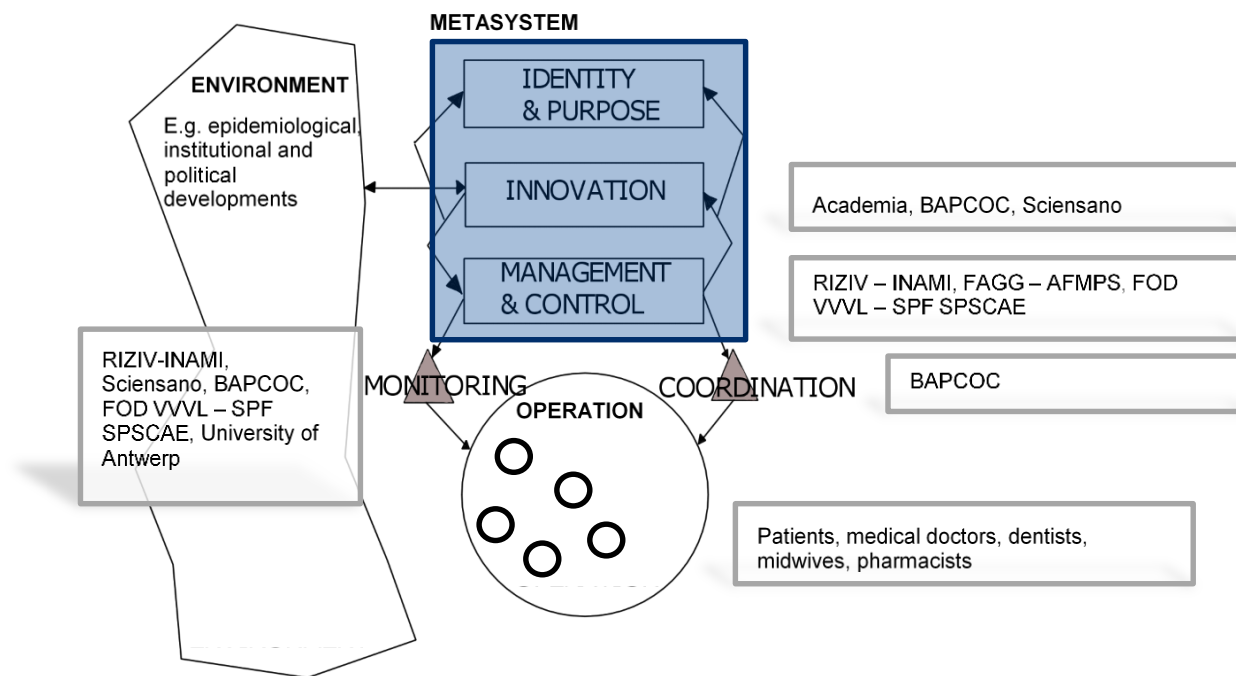
It is important to mention that as competences with regard to antibiotics and AMR are shared between the federal state (e.g. regulation and financing of the compulsory health insurance, legislation on professionals qualifications, registration and price control of pharmaceuticals, health workforce planning and forecasting, health of food-producing animals), the communities (e.g. training of physicians, dentists, veterinarians, quality control in acute hospitals, hospital accreditation, coordination in primary healthcare, health promotion and disease prevention, long-term care) and the regions (e.g. agriculture, the environment, health of wildlife, animal welfare), the actors involved are working in a three-level structure, an intricate situation. In the human sector for example, defining professionals' qualification is the competence of the federal minister of Social Affairs and Public Health, while handing out the recognitions is the responsibility of the federated (community) Minister of Health. As of 2018, animal health is the shared responsibility of the federal Minister of Small Businesses, the Self-employed, Small and Medium-sized Enterprises, Agriculture and Social Integration and the federal minister of Social Affairs and Public Health, except wildlife health which is the responsibility of the federated (regional) Minister of Environment, Nature and Agriculture. Animal welfare on the other hand is the competence of the federated (regional) Minister of Mobility, Public Works, Tourism and Animal Welfare.

3.4.2 Human sector

Figure 4 presents the main actors involved in antibiotic prescription and use in the human sector, inspired by the Viable Systems Model (VSM).



Figure 4 – The viable systems model applied to the human sector



3.4.2.1 Operations

System 1 is the operational level: the place where the core work is done. This is exactly the level where patients are prescribed antibiotics by their medical doctor or dentist (or midwives). We can distinguish two subfields: the ambulatory sector and the hospital sector. The main actors are patients, medical doctors, dentists and pharmacists. Guidelines on antibiotic prescribing for treatment and prophylaxis are available for medical doctors working in the ambulatory and hospital sector; they are discussed in section 6.1. For dentists there are currently no evidence based guidelines available. The determinants that influence the prescription of antibiotics for human use are described in section 5.1.

3.4.2.2 Coordination

The coordination function is performed by the **Belgian Antibiotic Policy Coordination Committee** (BAPCOC), which was founded in 1999; its composition and competences were laid down in the Royal Decree (RD) of 26 April 1999.⁷⁵ This RD was signed by the ministers in charge of public health and agriculture. Belgium was one of the first European countries to implement a national antibiotic policy coordinating commission. BAPCOC acts at the federal level.



The overall objective of BAPCOC is to promote the prudent use of antibiotics in humans and animals and to promote infection control and hospital hygiene, with the overall aim to reduce antibiotic resistance.⁷ BAPCOC's current governance is composed of a steering committee, working groups and the general assembly. The **steering committee** ('Bureau') includes the BAPCOC president and vice-president, chairs and vice-chairs of the working groups, experts from other partner institutions (e.g. Sciensano, cf. infra) and the support team; it meets at a monthly basis. The steering committee is responsible for the continuity, interaction and follow-up of initiatives and projects. The **working groups** cover ambulatory practice, hospital medicine, veterinary medicine, awareness raising and the federal hospital hygiene platform (responsible for hospital infection prevention and control). They coordinate initiatives promoting prudent antibiotic use in their respective field of expertise. The **support team** (i.e. scientific secretariat (1.7 FTE) supervised by a medical doctor who is responsible for the Quality & Patient Safety Division at the Federal Public Service Health, Food Chain Safety and Environment (FOD VVVL – SPF SPSCAE)) is responsible for BAPCOC's day-to-day management, and is hosted at the FOD VVVL – SPF SPSCAE. At **plenary meetings** of BAPCOC, which are held three times a year, the working groups report on their activities so that all stakeholders, incl. policy makers, scientific organisations, public health institutes are informed about the BAPCOC activities and results.⁷⁶

BAPCOC issued a **policy paper for the 2014-2019 term**, outlining policies to improve antibiotic use and appropriateness of antibiotic prescriptions in the hospital, outpatient and animal sector.⁷⁷ It does not only include targets for the various sectors (see Box 10), it also pays attention to e.g. quality measures and audits, training, monitoring of antibiotic stewardship in hospitals (see section 6.1.1.3).

In 2018, the **BAPCOC budget** (i.e. € 21.8 million) financed the following activities through the Budget of Financial Means (BFM)^q: hand hygiene campaigns (€ 125 000), hospital antimicrobial stewardship (€ 4 433 298) and IPC teams (€ 9 933 417 for nurses and € 7 087 188 for physicians), regional IPC platforms (€ 22 310), nosocomial information (€35 000). (FOD VVVL – SPF SPSCAE, *personal communication*) The (winter) 2017-2018 awareness campaign on the prudent use of antibiotics in the community (€ 400.000) were developed by BAPCOC but, similar to other national campaigns, they were implemented by the Offices of the Prime Minister. Until 2016, the development of guidelines and other research projects (€165 000) were financed through 'article 56' RIZIV – INAMI budgets^r.⁷⁸ (FOD VVVL – SPF SPSCAE, *personal communication*)

Box 10 – Targets defined in the BAPCOC Policy paper for the 2014-2019 term

For the hospital sector:

- Choice of therapeutic antibiotics following local instructions in at least 90% of cases;
- Indication statement of antibiotic therapy in the medical record in at least 90% of cases;
- Choice of surgical antibiotic prophylaxis following local instructions in at least 90% of cases;
- Duration of surgical antibiotic prophylaxis following local instructions in at least 90% of cases.

^q Each year the national hospital budget or Budget of Financial Means (BFM) is defined by Royal Decree. It is a closed-end budget covering non-medical activities, such as the services for accommodation, accident and emergency services, and nursing activities. It consists of several sub-budgets which are allocated to hospitals according to a large set of criteria and parameters.

^r The RIZIV – INAMI insurance committee ('Verzekeringscomité'/Comité de l'assurance') is authorized to conclude agreements to finance research on models for the provision and financing of medical care; they are often referred to as Article 56 budgets as it is described in Article 56 of the respective law of 1994.⁷⁸

**For the ambulatory sector:**

- A decrease in total antibiotic consumption, from more than 800 prescriptions per 1000 inhabitants per year today to 600 prescriptions by 2020 and 400 prescriptions by 2025;
- A decrease in quinolone consumption, from about 10% of the total antibiotic use today to 5% by 2018;
- An increase in ratio amoxicillin versus amoxicillin + clavulanic acid^s, from about 50/50 today to 80/20 by 2018.

For the veterinary medicine sector:

- Halving the use of antibiotics by 2020;
- Reducing by 75% the use of most critical antibiotics by 2020;
- Halving the use of medicated premixes containing antibiotics by 2017.

Source: BAPCOC Policy paper for the 2014-2019 term⁷⁷

Critical notes

From the many interviews with stakeholders we learnt that **BAPCOC's budget** is an emotive subject. This observation was also confirmed in the reports of the EC and ECDC team who performed an AMR country visit to Belgium (November 2017, see chapter 9).^{76, 80} The greater part of BAPCOC's financial resources are allocated to actions in the hospital sector, but what is more, because BAPCOC's budget is primarily sourced from public health funds, practical difficulties are experienced in allocating these funds to veterinary or One Health activities.⁸⁰ The Royal Decree of 1999 did not address the allocation of financial resources to different institutions or projects, which leads to difficulties to obtain money to start projects. As long

as the financing is ad-hoc and not structural, it is extremely difficult to set up any (long-term) policy.

Some stakeholders think that the governance of BAPCOC is **not transparent enough** (see chapter 7). To them it is unclear how decisions are taken, mandates are filled and budgets are allocated.

Another shortcoming of the current functioning of BAPCOC is the fact that everybody involved (with the exception of the support team), participates on a **voluntary basis**, which affects the persistence and continuity of BAPCOC's activities. At the moment, a lot of personal commitment of experts in the field with already full agenda's is required. Still, the work and dedication demonstrated so far are considerable; for a detailed description of BAPCOC's interventions, the reader is referred to section 6.1.

In order to get a real steering role in the field of antibiotic prescription and use and AMR, BAPCOC's support team should, according to some stakeholders, be **enlarged with a core group of high-level scientists** who prepare advises and recommendations.

Several BAPCOC members witnessed that BAPCOC receives **little recognition**. More precisely, in recent years several measures with regard to the prescription, delivery and/or reimbursement of antibiotics were taken (e.g. the shift of antibiotics delivered by pharmacies open to the public from category B to category C (see section 1.1.1.1)) without the consultation of BAPCOC, which will only serve to discourage the BAPCOC members.

Communication is another area for improvement: for instance, BAPCOC's website is not user-friendly (e.g. documents are difficult to find, functionalities are limited), misses links to important partners and is not kept up-to-date. Stakeholders complain that this has a detrimental effect on the visibility of BAPCOC's work (e.g. easy access to guidelines).

The Royal Decree of 1999 stipulated that the BAPCOC steering committee (bureau) would ensure a balance between the human and the animal sector.⁷⁵ As highlighted by the ECDC visit report,⁷⁶ the composition of the

^s Clavulanic acid is an example of a β -lactamase inhibitor. The combination of a β -lactamase inhibitor with amoxicillin extends the antibacterial spectrum of amoxicillin to some β -lactamase-producing microorganisms. The combination

amoxicillin-clavulanate should not be recommended in the first line, but only when the risk of β -lactamase-producing microorganisms is clearly increased.⁷⁹



Bureau included a president (in principle the general director of the health care administration of the FOD VVVL – SPF SPSCAE), a secretary, two medical doctors and two veterinarians designated by the respective ministers in charge of health and agriculture.⁷⁵ The vice presidency should turn every 18 months between two medical doctors and the two veterinarians. At the time of conducting this study, the vice-president was a medical doctor, and two out of the 13 members of the Bureau were veterinarians from the animal health sector.

Finally, the ECDC team who performed the AMR country visit to Belgium (see chapter 9) highlighted several **gaps** in the strategy (e.g. no attention for nursing homes, no targets for infection prevention and control) and specified that actions are somewhat **generic** and that **executive actors and resources are not clearly identified** and earmarked.⁷⁶

3.4.2.3 Management and control

System 3 activities regulate the operation, determine the performance levels and decide on resources allocated to achieve the desired performance level of systems 1 and 2. It may learn about the operation through formal audit processes and monitoring (system 3) or through direct communication with system 1 and 2. System 3 provides information on how this is working to system 4.^{72, 74}

The National Institute for Health and Disability Insurance (RIZIV – INAMI), the Federal Agency for Medicines and Health Products (FAGG – AFMPS) and the Federal Public Service Health, Food Chain Safety and Environment (FOD VVVL – SPF SPSCAE) are involved in the management and control with regard to the prudent use of antibiotics in Belgium.

Within the **National Institute for Health and Disability Insurance** (RIZIV – INAMI) several departments and commissions play a role in antibiotic policy. For instance, the *Commission for the Reimbursement of Pharmaceuticals* ('Commissie Tegemoetkoming Geneesmiddelen' – 'Commission de Remboursement des Médicaments' (CTG – CRM)) formulates proposals to amend the list of reimbursable pharmaceutical specialties (e.g. the inclusion of new pharmaceutical specialties, the modification of the reimbursement conditions of existing pharmaceutical specialties), gives advice at the request of the minister of Social Affairs and Public Health with regard to

policy aspects concerning the reimbursement of pharmaceutical specialties and formulates proposals to the Insurance Committee for interpretation rules concerning the reimbursement of pharmaceutical specialties.⁸¹

Within the *Medical Care Department* ('Dienst voor geneeskundige verzorging' – 'Le Service des soins de santé') there are several entities involved. The *Pharmaceutical Management Service* for instance organizes and directs the consultative bodies and their working groups (among others the Commission for the Reimbursement of Pharmaceuticals), supports the operation of the sector and analyses and interprets information from its databases.⁸² The *Medical Evaluation and Control Service* ('Dienst voor geneeskundige evaluatie en controle' – 'Le Service d'évaluation et de contrôle médicaux') has e.g. in 2007 performed a broader evaluation of the prescription of quinolones by general practitioners. The *Research, Development & Quality service* organizes the feedback to prescribers, which aims at informing physicians and dentists about their prescription behaviour; the feedback enables them to compare their own prescription behaviour with their peers (see section 6.1).

The *National Council for Quality Promotion* ('Nationale Raad voor KwaliteitsPromotie' – 'Conseil National de Promotion de la Qualité'), one of the councils within the Medical Care Department, chooses the priority themes to be addressed by the peer review and also the programmes to promote quality. It plays a role in the application of the legislation on the responsibility of health care providers and develops recommendations for a good use of the global medical file.⁸² With regard to antibiotic prescription and use, the National Council for Quality Promotion was consulted in the development and validation of indicators for the individual feedback to general practitioners. (RIZIV – INAMI, *personal communication*)

The **Federal Agency for Medicines and Health Products** (FAGG – AFMPS) is since 2007 the competent authority for medicines and health products in Belgium.⁸³ FAGG – AFMPS was thus installed after the foundation of BAPCOC (1999). The agency is responsible for the quality, safety and efficacy of medicines and health products. The promotion of responsible and correct use of antibiotics falls also under the competences of FAGG – AFMPS.⁸³ Its areas of expertise are described in Box 11. Just like RIZIV – INAMI, FAGG – AFMPS falls under the authority of the minister of Social Affairs and Public Health.



Within the FAGG – AFMPS several entities play a role in AB/AMR policy. The *Commission for Medicinal Products for Human Use* ('Commissie voor geneesmiddelen voor menselijk gebruik' – 'La Commission des médicaments à usage humain'), provides (among others) advice on applications for market authorisations and on scientific questions related to medicinal products. With regard to the rational use of antibiotics and in order to limit the development of resistance, the Commission can, for example, determine whether specific measures are needed to align the delivery of antibiotics with the recommendations of BAPCOC, such as limiting the delivery, granting customized packaging sizes for specific indications, or possibly allowing the fractionation of packaging. (FAGG – AFMPS, *personal communication*)

The *Belgian Centre for Pharmacotherapeutic Information* ('Belgisch Centrum voor Farmacotherapeutische informatie' – 'Centre Belge d'Information Pharmacothérapeutique'), which is under the governance of the FAGG – AFMPS, ensures the distribution of independent medicines information to healthcare providers. (FAGG – AFMPS, *personal communication*)

The *Task Force and working group 'unavailabilities'*, set up by the FAGG – AFMPS in collaboration with RIZIV – INAMI, pharmacists, hospital pharmacists, doctors, health insurance funds, pharmaceutical companies and distributors, reflects on how to tackle the problem of unavailabilities of medicines. (FAGG – AFMPS, *personal communication*; more details on the problems of unavailabilities can be found in section 8.1)

Box 11 – FAGG – AFMPS – areas of expertise

- Research and Development: FAGG – AFMPS evaluates, approves, monitors and checks the applications for clinical trials on medicinal and health products;
- Registration and market authorisation: FAGG – AFMPS evaluates new applications for registration or marketing authorization for medicines as well as requests for modification;
- Vigilance: FAGG – AFMPS monitors adverse effects associated with the use of medicines or health products through the collection of

information. It collects information, evaluates it and, if necessary, takes action.

- Production and distribution: FAGG – AFMPS controls the manufacturing, distribution, delivery, import and export of medicines and health products, and issues authorisations under the legislation. It also controls the conduct of pharmacies and fights against illegal practices.
- Proper use: FAGG – AFMPS ensures that patients have access to relevant information so that medicines and health products are used correctly. The agency is also developing and implementing public awareness campaigns to promote the proper use of medicines, and controls the advertising of medicines and health products.

Source: <https://www.fagg.be/nl/> (last access: 20 September 2018)

BAPCOC is seated within the **Federal Public Service Health, Food Chain Safety and Environment** (FOD VVVL – SPF SPSCAE). The FOD VVVL – SPF SPSCAE is involved in activities (e.g. surveys, activity reports) about clinical pharmacy, which have illustrated that the hospital pharmacists have developed various activities in order to support the proper use of antibiotics. In addition, the FOD VVVL – SPF SPSCAE is in charge of the quality improvement programme Pay for Performance (P4P; <https://www.health.belgium.be/en/node/33526>), in which also attention is given to the prudent use of antibiotics (see section 6.1.1.3). Last but not least, the FOD VVVL – SPF SPSCAE represents Belgium at the international level (e.g. EU, WHO, ECDC, Organisation for Economic Co-operation and Development (OECD)).



3.4.2.4 Audit and monitoring

These are the activities that monitor the performances of system 1 ('Operations') to help system 3 ('Management and control') perform its control function. The monitoring of the prescription and use of antibiotics is organised separately for the ambulatory and hospital sector.

Ambulatory sector

In order to monitor the sale of pharmaceutical products (a.o. antibacterial drugs) reimbursed by the compulsory health insurance and delivered by the pharmacies open to the public, the database Farmanet – Pharmanet was created in 1996 by **RIZIV – INAMI**.⁷⁸

RIZIV – INAMI uses Farmanet – Pharmanet data to provide feedback on prescription behaviour, i.e. to inform physicians and dentists about their prescription behaviour and that of the group of prescribers they belong to (e.g. doctors of a particular specialty). In this way, they can compare their own prescription behaviour with peers (benchmarking). Further details on Farmanet – Pharmanet can be found in section 4.2.1.1; in chapter 6 more details can be found on the feedback and its impact.

Hospital sector

Sciensano plays a crucial role in monitoring the prescription and use of antibiotics in the hospital sector. In 2017, two sister institutions, the Scientific Institute of Public Health (WIV – ISP) and the Veterinary and Agrochemical Research Centre (CODA – CERVA), merged into Sciensano. Sciensano is based on the One Health concept whereby human health, animal health and environmental management are intrinsically linked.

In 2007, the Antibiotic Use in Hospitals (ABUH) project, a national surveillance system on the use of systemic antibacterial agents, was installed; it was managed by Sciensano. Participation was one of the requirements for hospitals receiving funding for antibiotic stewardship (see section 6.1.1.3).⁸⁴ In 2013 the ABUH project was replaced by BeH-SAC, which stands for 'Belgian Hospitals - Surveillance of Antimicrobial Consumption'. Data are no longer provided by the hospitals themselves, but transferred directly from RIZIV – INAMI to Sciensano.

In addition, Sciensano is also the national focal point for the **European Surveillance of Antimicrobial Consumption** (ESAC-net; see section

4.2.1), a Europe-wide network of national surveillance systems coordinated by the European Centre for Disease Prevention and Control (ECDC).⁸⁵ The data are collected through annual data calls. For Belgium the data on the use of antimicrobials for systemic use in the hospital and ambulatory sector (based on reimbursement data) are collected by RIZIV – INAMI, and then transferred to and validated by Sciensano. In the validation phase, BAPCOC as well as the University of Antwerp (Laboratory of Medical Microbiology) are involved.

The national coordination team of the **ECDC point prevalence surveys** (PPS, see Box 18) of healthcare-associated infections and antimicrobial use in acute care hospitals and the Global PPS of antimicrobial consumption and resistance in acute care hospitals (see section 4.2.1.2) comprises collaborators from Sciensano, the FOD VVVL – SPF SPSCAE and the University of Antwerp. Data on the prevalence of healthcare-associated infections and antimicrobial use in residents of long-term care facilities are collected by the ECDC HALT project (see section 4.2.1.2); in Belgium data collection is coordinated by Sciensano (see also <http://www.nsih.be/>).

3.4.2.5 Intelligence and innovation

Information from outside the system is picked up, interpreted and feeds into the activities of system 1 ('Operations') and 3 ('Management and control'), and informs the decision-making.^{72, 74} These activities are mostly performed by academia, but also by BAPCOC and Sciensano. Their scientific work consists of e.g. the analysis of and reporting on prescription and use data.

3.4.2.6 Policy, identity and purpose

System 5 reflects on the system's governing purposes, defines and communicates the overall values that determine the identity of the system. In addition, it decides on resource allocation between systems 3 ('Management and control') and 4 ('Intelligence and innovation').^{72, 74}

Currently we could not identify an actor fulfilling the system 5 functions in the human sector.



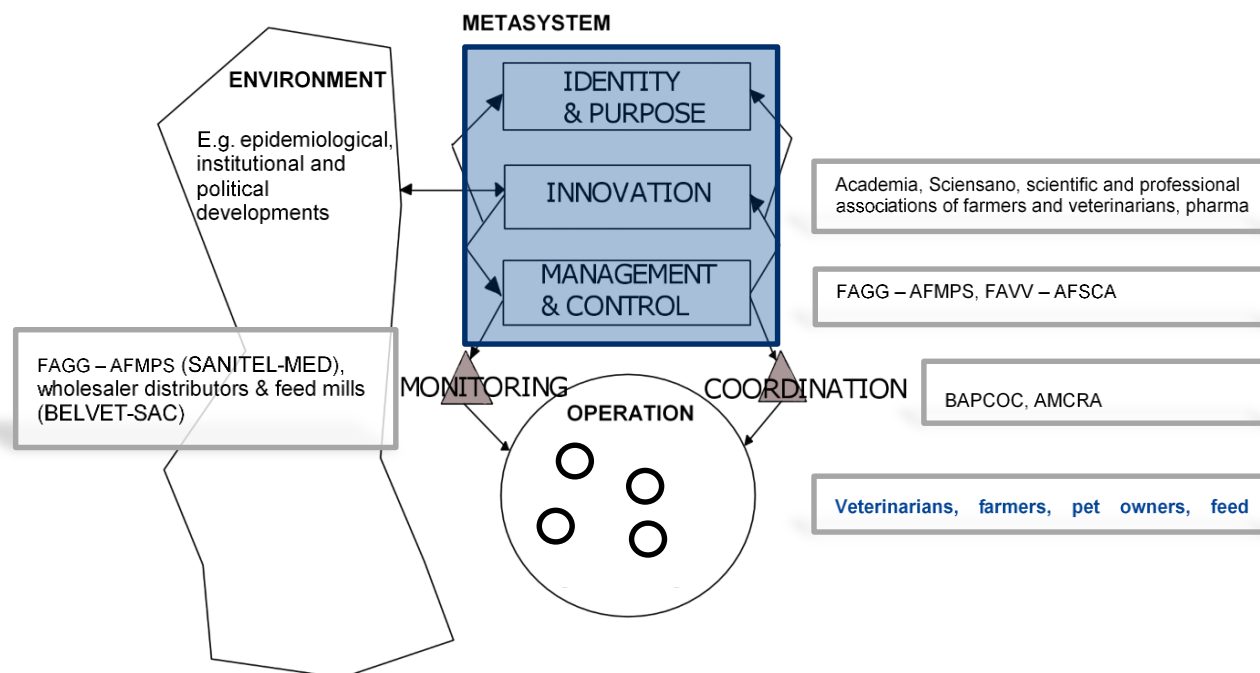
3.4.2.7 Environment

The environment encompasses epidemiological, institutional and political developments in the wider health care system.

3.4.3 Veterinary sector

Figure 5 presents the main actors involved in veterinary antibiotic prescription and use, inspired by the Viable Systems Model (VSM) as an organising principle (see Box 9). The five systems within the VSM are further explained through the example of antibiotic prescription and use in the veterinary sector in Belgium.

Figure 5 – The viable systems model applied to the veterinary sector





3.4.3.1 Operations

System 1 is the operational level. This is the field of **animal owners** and **veterinarians** differentiated in two subfields: the sector of companion animals on the one hand, and food-producing animals on the other hand. In the former the actors are pet owners and veterinarians. In the latter, farmers, veterinarians and feed producing companies are the main actors prescribing, selling and using antibiotics to treat animals. This subfield is more complex because in addition to animal health and welfare, economic interests and food safety issues come into play. Farmers are farm managers, calling a veterinarian when they suspect a health problem in one (or more) animals. Veterinarians diagnose ill animals, prescribe and sell drugs to farmers. In their treatment decisions, veterinarians can rely on the formularies and guidelines for prudent antibiotic use developed by the Belgian Centre of Expertise on Antimicrobial Consumption and Resistance in Animals (AMCRA) (see section 3.4.3.2). Veterinarians initiate treatments, but farmers are allowed to do the follow-up treatment (see section 3.2.2).

3.4.3.2 Coordination

The coordination function is performed by the Belgian Antibiotic Policy Coordination Committee (BAPCOC; see section 3.4.2.2) and the **Centre of Expertise on Antimicrobial Consumption and Resistance in Animals (AMCRA)** AMCRA. As was explained above, BAPCOC has several working groups among which one on veterinary medicine. The veterinary sector is represented in the BAPCOC bureau with three representatives, among whom the president of AMCRA (cf. infra). AMCRA is also represented in the veterinary working group of BAPCOC.

In 2012 AMCRA was founded. Its main objective is to reduce antibiotic use in animals through advice, the diffusion of formularies, guidelines and awareness raising among veterinarians, farmers and the general public.¹⁵ For that purpose 10 goals have been proposed (see Box 12).

AMCRA's communication and sensitisation activities are mainly (70%) financed by FAVV – AFSCA and FAGG – AFMPS. The remaining 30% is contributed by some of the stakeholders such as the Belgian farmers' unions, the Belgian Feed Association (BFA) and the pharmaceutical sector organization (pharma.be). Its scientific work is financed by clients

demanding data analyses, e.g. FAGG – AFMPS for the SANITEL-MED data (see section 3.4.3.4).

On 30 June 2016, 3 AMCRA 2020 goals (i.e. a 50% reduction of antibiotic use by 2020, a 75% reduction of the most critical antibiotics by 2020, and a 50% reduction of feed medicated with antibiotics by 2017) have been ratified by an agreement between the Belgian Federal Government, represented by the Minister of Agriculture and the minister of Social Affairs and Public Health, and the stakeholders.⁸⁶

Box 12 – AMCRA's 2020 goals

1. 50% lower antibiotic use by 2020
2. 75% lower use of the most critical antibiotics by 2020
3. 50% lower use of feed medicated with antibiotics by 2017
4. A global data collection system by 2016
5. A plan for each farm
6. Benchmarking of farmers and veterinarians
7. No antibiotics for prophylaxis, promotion of alternatives
8. Awareness-raising, repeatedly
9. Transparency and monitoring of suppliers and users
10. Surveillance of resistance to antibiotics

Note: reference year is 2011

Source: <https://www.amcra.be/fr/amcra-vision-2020/> (last access: 27 February 2019)

AMCRA has been explicitly assigned the facilitation and coordination of the actions undertaken by the stakeholders and government to achieve the goals of the agreement, which runs up to 31 December 2020. In section 6.2, the interventions that have already been executed or that are running, are described in more detail.



3.4.3.3 Management and control

The **Federal Agency for Medicines and Health Products** (FAGG – AFMPS; see section 3.4.2.3), the Federal Agency for the Safety of the Food Chain (FAVV – AFSCA) and the Federal Public Service Public Health, Food Chain Safety and Environment (FOD VVVL – SPF SPSCAE) co-regulate initiatives with regard to the prudent use of antibiotics and AMR.⁵⁷

The **Federal Agency for the Safety of the Food Chain** (FAVV – AFSCA) was founded in 2000, as a result of the ‘dioxine crisis’^t. Its core business is to guard the safety and quality of food in order to protect the health of humans, animals and plants. FAVV – AFSCA falls within the authority of the Minister of Small Businesses, Self-employment, Small and Medium-sized Enterprises, Agriculture and Social Integration.

As was described above, both FAGG – AFMPS and FAVV – AFSCA finance the AMCRA sensitisation activities, but they are also represented in the AMCRA steering committee. In addition, the FAGG – AFMPS collects the taxes on antibiotics (see section 6.2.2.1) which are used to finance initiatives with regard to the prudent use of antibiotics and the antibiotic use monitoring and feedback.

The **Federal Public Service Public Health, Food Chain Safety and Environment** (FOD VVVL – SPF SPSCAE), and more specifically, the Directorate General Animals, Plants and Foods is (also in a European context) involved in the regulations on the manufacture and placing on the market and use of medicated feed (including medicated feed containing antibiotics) and on additives for use in animal nutrition. The Directorate General Animals, Plants and Foods is also involved in the regulations relating to the conditions of use of medicines (including antibiotics) by veterinary doctors and animal owners (e.g. the Royal Decree of 21/7/2016 which defines the respective obligations of the veterinarian and the person in charge of the animals during the use of medicines, obligations which make it possible to ensure the traceability of this use since the deposit of the veterinary drug until its use on the animal). Last but not least, this Directorate

General also plays a role in the regulations relating to food standards/food chain safety, including food contaminants constituted by antimicrobial resistant micro-organisms. More precisely, it participates in the ad hoc codex alimentarius^u intergovernmental task force on Antimicrobial Resistance which works on the revision of the Code of Practice to Minimize and Contain Antimicrobial Resistance and on the revision of Guidelines on Integrated Surveillance of Antimicrobial Resistance. This work is done in collaboration with WHO and OIE. (FOD VVVL – SPF SPSCAE, *personal communication*)

3.4.3.4 Audit and monitoring

For the databases **Belgian Veterinary Surveillance of Antimicrobial Consumption (BelVet-SAC)** and **SANITEL-MED** information is extracted from system 1 (‘Operations’) to help system 3 (‘Management and control’) to perform its management and control function. FAGG – AFMPS coordinates these data collection efforts in collaboration with BAPCOC and the faculty of veterinary medicine of Ghent University. Data are provided by the wholesaler-distributors and feed mill companies for BelVet-SAC, and the veterinarians and farmers for SANITEL-MED. BelVet-SAC includes antibiotic use data for both food-producing and companion animals. SANITEL-MED is the national register for all prescribed, supplied and administered antibiotics used in food-producing animals. Both data systems are described in detail in section 4.2.2.

^t The ‘dioxin crisis’ was a food scandal that broke out in Belgium in the spring of 1999, when toxic dioxins were found to have entered the food chain.

^u The Codex Alimentarius develops international standards and guidelines for food and food security, but also in related areas, such as hygiene and labelling.



3.4.3.5 Intelligence and innovation

Information from outside the system is picked up, interpreted and feeds into the activities of system 1 ('Operations') and 3 ('Management and control'), and informs the decision-making body.^{72, 74} These activities are mostly performed by academia in general, but also **AMCRA** has a scientific unit which performs among others the analysis of and reporting on the SANITEL-MED data.

In addition, the Department of Infectious Diseases in Animals of **Sciensano** (see section 3.4.2.4) is contributing to this function^v. As nation-wide coordinator of public health activities, Sciensano represents Belgium in various international bodies active in those fields (e.g. European Food Safety Authority (EFSA), World Organisation for Animal Health (OIE, Office International des Epizooties), WHO, ECDC).

3.4.3.6 Policy, identity and purpose

Currently we could not identify an actor fulfilling the system 5 functions in the veterinary sector.

3.4.3.7 Environment

The environment encompasses epidemiological, institutional and political developments in the wider health care system.

Key messages

- As competences with regard to antibiotics and AMR are shared between the federal state, the communities and the regions, the actors involved are working in a three-level structure, an intricate situation.
- Since 1999, the coordination of Belgian antibiotic policy has been performed by BAPCOC. The work and dedication demonstrated so far are considerable. Yet, BAPCOC's composition, mandate and tasks need to be adapted to current needs and approaches. For instance, the involvement of the veterinary sector should be improved.
- The National Institute for Health and Disability Insurance (RIZIV – INAMI), the Federal Agency for Medicines and Health Products (FAGG – AFMPS) and the Federal Public Service Health, Food Chain Safety and Environment (FOD VVVL – SPF SPSCAE) are involved in the management and control with regard to the prudent use of antibiotics in the human sector.
- Sciensano plays a crucial role in monitoring the prescription and use of antibiotics in the hospital sector. In the ambulatory sector, the monitoring of antibiotics can be done through the database Farmanet – Pharmanet, created by RIZIV – INAMI.
- In the veterinary sector, there are two important subfields at the operational level: the sector of the companion animals on the one hand, and the sector of food-producing animals on the other hand. In the latter, economic interests play an important role.
- Since its foundation in 2012, AMCRA has played a major role in the coordination of activities with regard to the prudent use of antibiotics in the veterinary sector.

^v <https://www.sciensano.be/en/about-sciensano/sciensanos-organogram/infectious-diseases-animals>



- The Federal Agency for Medicines and Health Products (FAGG – AFMPS), the Federal Agency for the Safety of the Food Chain (FAVV – AFSCA) and the Federal Public Service Public Health, Food Chain Safety and Environment (FOD VVVL – SPF SPSCAE) co-regulate initiatives with regard to the prudent use of antibiotics and AMR.
- FAGG – AFMPS coordinates the antibiotic use data collections BelVet-SAC (food-producing and companion animals) and SANITEL-MED (only food-producing animals), in collaboration with BAPCOC and the faculty of veterinary medicine of Ghent University.
- Nor in the human, neither in the veterinary sector, we could identify an actor fulfilling the policy, identity and purpose functions as described in the VSM.

4 ANTIBIOTIC USE AND ANTIMICROBIAL RESISTANCE

4.1 How to measure antibiotic use

4.1.1 Human sector

4.1.1.1 International drug utilization measures and their applications

Variables to measure drug use, such as cost, number of units, number of prescriptions, or physical quantity of drugs, can vary between regions and countries over time and thus limit comparisons of drug use at an international level. To address these issues, a technical unit of measurement, the Defined Daily Dose (DDD) was created (see Box 13).⁸⁷ The Anatomical Therapeutic Chemical (ATC) classification system (see Box 6) and the Defined Daily Dose (DDD) as a measuring unit have become the gold standard for international drug utilization monitoring and research.⁸⁸

Box 13 – International drug utilization measures and their applications

The **defined daily dose (DDD)** is the assumed average maintenance dose per day for a drug used for its main indication in adults.⁸⁸ DDDs are standardized doses provided as part of the Anatomical Therapeutic Chemical drug classification system maintained by the WHO Collaborating Centre for Drug Statistics Methodology (www.whocc.no/atcddd).⁸⁹ The DDD is an internationally accepted unit for measuring medicine use and for making comparisons between countries.

The DDD does not necessarily reflect the recommended or **Prescribed Daily Dose (PDD)**, see below) in the specific country. Only one DDD is assigned per ATC code and route of administration (e.g. oral intake). The DDD is sometimes a 'dose' that is rarely if ever prescribed, because it might be an average of two or more commonly used doses and is based on an adult body weight of 70kg.⁹⁰ However, DDDs provide a fixed unit of measurement independent of price, currencies, package size, strength (i.e. amount of drug per unit) and molecule, as one day of treatment



receives approximately equal weight whatever the drug.⁹¹ This enables the researcher to assess trends in drug use and to perform comparisons between population groups.⁸⁸

DDDs per 1000 inhabitants per day (**DID**) may provide a rough estimate of the prevalence of the study population treated on a certain day with a particular drug or group of drugs. For instance, 20 DDDs per 1000 inhabitants per day indicates that 2% of the population on average might receive a certain drug or group of drugs on a certain day. This estimate is most useful for chronically used drugs when there is a good agreement between the average prescribed daily dose (cf. supra) and the DDD.

The **prescribed daily dose** (PDD) is defined as the average dose prescribed according to a representative sample of prescriptions; it will give the average daily amount of a drug that is actually prescribed. The PDD can be determined from studies of prescriptions or medical or pharmacy records.⁸⁸

Drug use by patients in *ambulatory care* can also be expressed by **number of packages** that may be expressed per 1000 inhabitants per day (PID).^{92, 93} Numbers of packages may be used at national level as a proxy for the number of prescriptions, provided that one antibiotic package is prescribed per prescription encounter.

Some more metrics have been proposed to express antibiotic use in the ambulatory sector, such as the number of treatments or prescriptions and the number of treated individuals.⁹³ These last two metrics are independent of the prescribed dose, and can also be expressed per 1000 inhabitants per day. The number of treated individuals is considered to be a very relevant measure when relating antibiotic use to antimicrobial resistance.⁹³ The number of prescriptions per 1000 inhabitants is an indicator used by BAPCOC to set national targets for ambulatory care.

Drug use in *hospitalised patients* is most often expressed as **DDDs per 100 (occupied) bed-days or patient-days**. For example, the average use of 80 DDD per 100 bed-days in a surgery ward indicates that 80% of these patients might receive a DDD of an antibiotic every day.⁹⁴ The unit DDDs per 100 bed-days is quite useful for benchmarking between hospitals. However, the definition of a bed-day may differ between hospitals or countries, and bed-days should be adjusted for occupancy

rate. It is thus important that the same definition is used when performing comparative studies. Other common indicators are inpatient DDDs per 1000 admissions to estimate the proportion of patients exposed to antibiotics, inpatient DDD per 1000 inhabitants (less relevant for hospital care but used in ECDC reports), and the prevalence of inpatients with at least one antibiotic (antimicrobial), usually measured in point prevalence surveys (PPS, see section 4.2.1.2).

For drugs normally used for short periods (like antibiotics), the data are often presented as numbers of **DDDs per inhabitant per year**. It gives an estimate of the average number of days for which each inhabitant is treated annually. For instance, an estimate of 5 DDDs per inhabitant per year indicates that the utilization is equivalent to the treatment of every inhabitant with a five-day course during that year.

Expressing drug utilization in terms of **grams of active ingredients**, should be performed with caution as drugs with low potency will account for a larger fraction of the total than drugs with high potency. Combined products may also contain different amounts of active ingredients from plain products, and this difference will not be reflected in the figures.

Caution is also indicated when counting **numbers of tablets**, as it does not reflect the variations in strengths of tablets, with the result that low-strength preparations contribute relatively more than high-strength preparations to the total numbers. Also, short-acting preparations will often contribute more than long-acting preparations.

The counting of **prescriptions** is valuable in measuring the frequency of prescriptions and in evaluating the clinical use of drugs (e.g. diagnosis and dosages used). However, it should be realised that numbers of prescriptions do not accurately reflect total use, unless total quantities of drugs per prescription are also considered.

Source: *Introduction to Drug Utilization Research*, WHO, 2003⁸⁷



One final remark: antibiotic use estimated from reimbursement data can be substantially lower than when estimated from sales data.^{95, 96} However in Belgium the difference was small as the reimbursement data for 2015 corresponded to 87% of the sales data; when expressed in DDD the proportion was 89%. (RIZIV – INAMI, *personal communication*)

4.1.1.2 The Daily Dose of Administration (DDA) - A Belgian measure for antibiotic use

Because of the concern that the DDDs do not always correspond to the doses prescribed or recommended in Belgium (DDD may deviate from the dose used for an indication in function of individual characteristics (e.g. age, weight) or pharmacokinetic reasons (e.g. renal failure)), RIZIV – INAMI published in 1997 a list of **Daily Doses of Administration** (DDAs) for antibiotics.⁹⁷ Although the DDAs have been developed as part of the information campaign to hospitals regarding antimicrobial products,⁹⁸ the index DDA is also used to describe antibiotic use in the ambulatory sector.⁹⁷

A DDA is the average daily dose that is administered in Belgium. Unlike the DDD, the DDA exists for each form and each dosage of the same active ingredient, which makes it possible to make correct estimates of the number of patients subjected to a given treatment.⁹⁹ It is argued that the DDA takes better account of the mode of administration and the concentration of the drug and its different packages.^{100, 101} The initial DDA list has been revised by the Francophone Association of Hospital Pharmacists from Belgium (AFPHB) and the BAPCOC working group on Hospital Medicine.⁹⁹

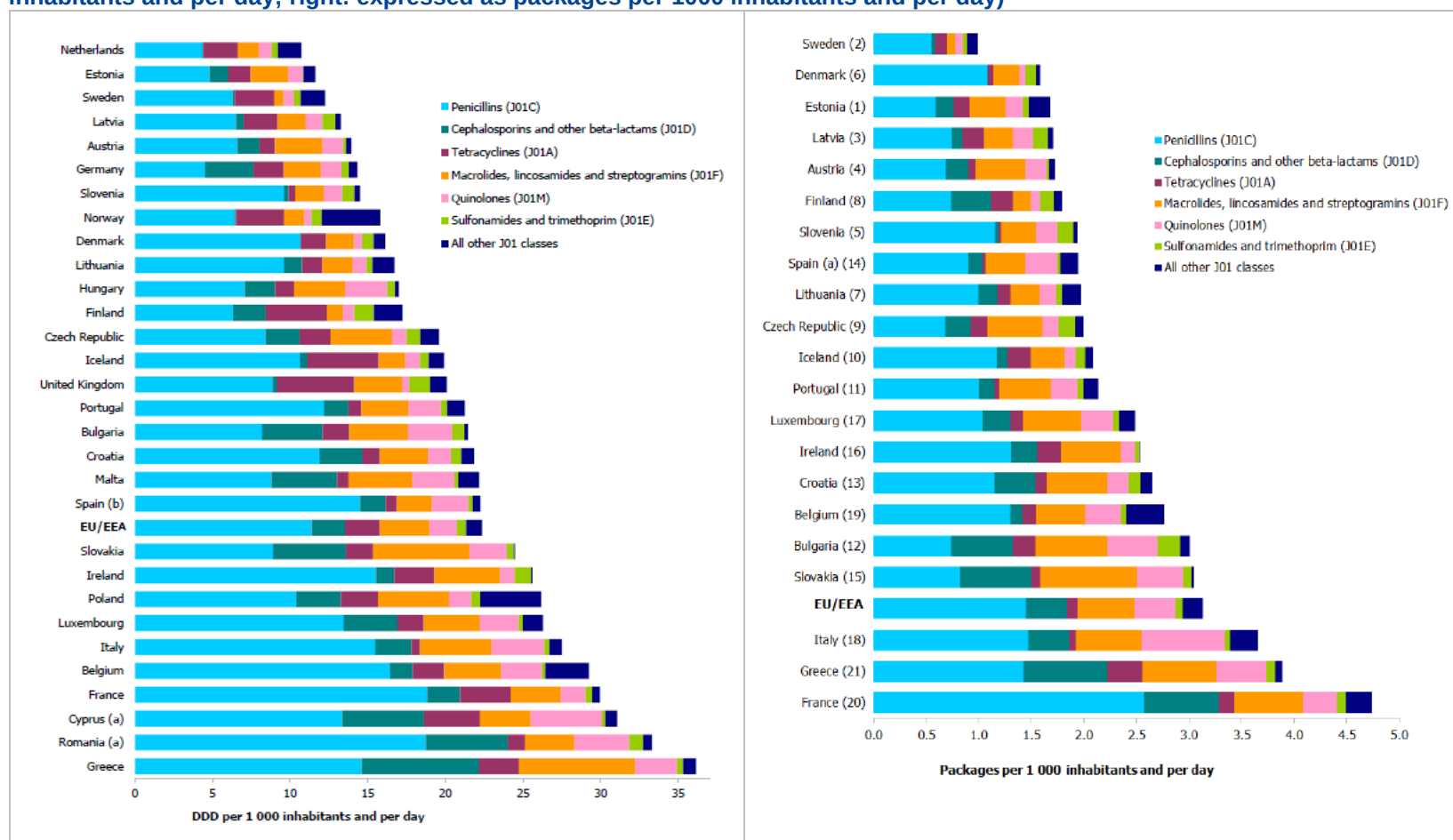
4.1.1.3 Which metric and indicator to be used?

It is currently **not clear yet which metric and indicator correlate(s) best with antibiotic-associated risks** such as resistance pressure.⁸⁹

Currently **experts disagree** on the most appropriate indicator to assess antibiotic use in ambulatory care over time and to measure the impact of interventions: is it the **DID or the PID?**^{90, 92, 93, 102, 103} This debate is complicating the monitoring of ambulatory antibiotic use because several studies showed diverging results depending on the indicator used (DID vs. PID), leading thus to contradictory conclusions.¹⁰²⁻¹⁰⁴ When looking for instance at the ESAC-net 2015 surveillance data for the ambulatory sector (see section 4.2.1), where countries are sorted from smallest to highest users (Figure 6)^w Belgium ranks 16th out of 21 countries when antibiotic use is expressed as PID, but only 26th out of 30 countries when expressed in DID.^{92, 106} (*Note:* At the time of publication, the 2017 PID data were not available. Therefore, we make that comparison based on the 2015 data.)

^w Up to 2016, the amount of antibiotics used in the community was expressed as DID and PID in the ESAC-net reports,¹⁰⁵ but from 2017 onwards the PID data are no longer presented in the yearly report.⁸

Figure 6 – Use of antibiotics for systemic use in the ambulatory sector by antibiotic group, EU/EEA countries, 2015 (Left: expressed in DDD per 1000 inhabitants and per day; right: expressed as packages per 1000 inhabitants and per day)



The EU/EEA bar refers to the corresponding population-weighted mean use. The numbers in parentheses (figure right) indicate the ranking of each of the 20 countries when use of antibiotics for systemic use in the ambulatory sector is expressed as 'DDD per 1000 inhabitants and per day' (see figure left).

(a) Cyprus and Romania provided total care data (i.e. including the hospital sector). (b) Spain provided reimbursement data (i.e. not including use of antibiotics obtained without a prescription and other non-reimbursed courses).

Source: Summary of the latest data on antibiotic use in the European Union - ESAC-Net surveillance data November 2016¹⁰⁶



The DDD as measurement unit has many advantages (see Box 13), but has also some limitations, e.g. antibiotic use in children expressed in DDD or DID is underestimated as the DDD metric only takes the dosage used in adults into account.⁹² As said before, it also does not always correspond to the dose used in routine practice, nor to the dose effectively received by the patient. Furthermore, the daily dosage of some antibiotics increased in Belgium, particularly for β -lactams, while the DDD did not, leading some authors to consider the number of packages as a more appropriate measure of ambulatory antibiotic use.^{93, 103} The number of DDD per package also

varies between countries, as is illustrated in Table 3. The use of e.g. 1000 DDD per year corresponds in the Russian Federation with 300 packages per year, but with 90 packages per year in Belgium.⁹² At last, the analyses of the trend of outpatient antibiotic use over time (2000-2008) for 31 countries expressed in DID and PID indicated that there was not only an increase in DDD per package over time (a yearly increase ranging between 0.04 and 0.31 DDD per package), but also that the change in DDD per package over time varied among countries, except for the urinary antiseptics (J01X).¹⁰²

Table 3 – Number of DDD per package

	Italy	Russian Federation	Bulgaria	Estonia	Lithuania	Greece	The Netherlands	Ireland	Portugal	Denmark	Finland	Belgium	Sweden
DDD/package	2.6	3.0	5.7	6.5	6.6	7.3	7.4	8.6	9.0	9.3	9.5	10.9	11.8

The number of DDD per package was calculated by dividing DID by PID values per country; for the majority of countries 2009 data were used, but for Italy 2008 and for Ireland 2007 data were used.

Source: Adriaenssens et al., 2011⁹²

Yet, antibiotic use expressed in **packages** also has important **limitations**. Not all European countries are able to provide this type of data; in the UK and the Netherlands for instance antibiotics are not dispensed in standard pack sizes, but as single units dispensed exactly following the doctor's prescription (see also section 8.2).⁹² Packages have been used as a proxy for prescription but it should be realised that sometimes only half of the pack is needed, while in other circumstances two or more standard packs are necessary. Hundred packages per year may correspond to 100 persons treated per year (1 package per person treated) but could also be equal to 50 persons treated (2 packages per person treated). Last but not least, also package sizes may change over time, according to commercial interest or to guidelines proposing higher dosages e.g. to treat infections with antibiotic-resistant bacteria (e.g. β -lactams to treat pneumococci with intermediate resistance to penicillin).⁹² In Belgium, the content of an average package increased in the period 2000-2010 both by strength and size, i.e. doubling the tablets for the most popular β -lactams.¹⁰³ Some authors thus suggest

that the increase in DID in Belgium is a more objective measure of the changes in antibiotic use than the decrease in PID.¹⁰³

Because **each measure has his limitations**, several authors have suggested to **combine different measures** for antibiotic use surveillance.^{90, 92, 93} Each measure may present related but different aspects of antibiotic use that are relevant with respect to antimicrobial resistance.⁹³

The aim of the Innovative Medicines Initiative (IMI) project 'Driving reinvestment in research and development and responsible antibiotic use' (DRIVE-AB) was 'to identify consensually validated quantity metrics for antibiotic use in the outpatient setting', by conducting a systematic literature review of drug use indicators and achieving consensus in a multidisciplinary international stakeholder panel, using a modified Delphi procedure.⁹⁰ The final set of five selected metrics included DDD per defined population, treatments/courses per defined population, treatments/courses per physician contact, prescriptions per defined population, prescriptions per



physician contact and seasonal variation of total antibiotic use. The metric packages was rejected.⁹⁰

4.1.1.4 Quality indicators for antibiotic use

An effective stewardship programme requires the ability to measure the appropriateness of antibiotic use in individual patients (see Box 24). Many quality indicators for appropriate antibiotic use have been developed.¹⁰⁷

ESAC (i.e. predecessor of ESAC-net) published in 2007 a set of 12 drug-specific quality indicators for outpatient antibiotic use in Europe.¹⁰⁸ These indicators were intended to better describe antibiotic use in ambulatory care and to assess the quality of national antibiotic prescribing patterns in Europe; they are especially relevant for policy makers. The indicators are presented in Table 4 (section 4.3.1), together with the results for 2017 reported by ECDC (ESAC-Net interactive website, 2019¹⁰⁹).

The ECDC, the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) have jointly established a list of 15 harmonized outcome indicators to assist EU member states in assessing their progress in reducing the use of antimicrobials and antimicrobial resistance in both humans and food-producing animals.¹¹⁰ There are 4 primary indicators, monitoring essential points, and 11 secondary indicators, monitoring highly recommended points to assess progress made in member states' action plans. The indicators with regard to antibiotic use in humans are presented in Box 14.¹¹⁰

Box 14 – ECDC/EFSA/EMA outcome indicators for use of antibacterials for systemic use (ATC group J01) in the human sector

Primary indicator:

Total consumption of antibacterials for systemic use (DDD per 1000 inhabitants and per day)

Secondary indicators:

Ratio of the consumption of broad-spectrum penicillins, cephalosporins, macrolides (except erythromycin) and fluoroquinolones to the consumption of narrow-spectrum penicillins, cephalosporins and erythromycin;

Proportion of total hospital AMC that are glycopeptides, 3rd- and 4th-generation cephalosporins, monobactams, carbapenems, fluoroquinolones, polymyxins, piperacillin and enzyme inhibitor, linezolid, tedizolid and daptomycin (DDD per 1000 inhabitants and per day).

Source: <https://ecdc.europa.eu/en/publications-data/ecdc-efsa-and-ema-joint-scientific-opinion-list-outcome-indicators-regards>¹¹⁰

4.1.2 Veterinary sector

4.1.2.1 International drug utilization measures and their applications

Just like in human medicine, various indicators are used to quantify antibiotic use in veterinary medicine, e.g. the mg/PCU, the Defined Daily Dose for Animals (DDDvet) per 1000 animals and per year, the Defined Course Dose for Animals (DCDvet) per 1000 animals and per year (see Box 15),¹¹¹ and likewise results can differ substantially depending on the method used. The selection of the indicator should be based on the study objective.¹¹² The presentation of the data on drug use in veterinary medicine is based on the ATCvet system (see Box 16).



Box 15 – International drug utilization metrics in veterinary medicine

The **mg/PCU** is a theoretical measurement unit developed by the European Medicines Agency (EMA) in 2009 and adopted across Europe.¹¹³ The 'mg' refers to the active ingredient weight in milligrams of all antibiotics used by food-producing species. The PCU refers to the 'Population Correction Unit' and takes into account a country's animal population over a year, along with the estimated weight of each particular species at the time of treatment with antibiotics.¹¹³ For instance, a 60 mg/PCU for food-producing animals means that on average, and over the course of a year, 60 mg of active antibiotic ingredient was used for every kg of bodyweight at the time of treatment.

The **defined daily dose for animals** (i.e. the assumed average dose per kg animal per species per day, abbreviated as DDDvet) and the **defined course dose for animals** (i.e. the assumed average dose per kg animal per species per treatment course, abbreviated as DCDvet) for antimicrobial agents for use in cattle, pigs and broilers* have been assigned according to the principles laid out in the 'Principles on assignment of defined daily dose for animals (DDDvet) and defined course dose for animals (DCDvet) (EMA/710019/2014)'.¹¹¹ The main aim of establishing the DDDvet and the DCDvet for antimicrobial veterinary medicinal products (VMP) was to provide standardised fixed units of measurement for the reporting of data on use by species that take into account differences in dosing, and hence to facilitate comparison between countries.¹¹⁴ Data on dosing (daily dose and number of days of treatment) obtained from Summaries of Product Characteristics (SPCs) for antimicrobial veterinary medicinal products were provided for broilers, cattle and pigs by nine EU countries (i.e. Czech Republic, Denmark, Finland, France, Germany, the Netherlands, Spain, Sweden and United Kingdom[§]), using a predesigned template. These nine countries covered approximately 65% of the food-producing animals in the EU in 2012.¹¹⁴

*: Data were originally collected for broilers, but values can be used as a proxy for other poultry species)

§: Seven countries delivered data on dosing for intramammary products (for lactating cows (LC) and dry cow treatment (DC)); of these, six countries also delivered data on dosing for intrauterine products as the seventh country did not have intrauterine products marketed.¹¹⁴

In veterinary medicine the **population at risk** is described in terms of **biomass** (or live weight) at risk of being treated, which is calculated by the product of the number of individuals at risk of being treated and a standard body weight (which can be a standard weight at treatment or a standard weight of live or slaughtered animals). The main advantage of using biomass is that it allows different animal species to be combined within the same population.^{5, 112} Yet, it has been questioned whether biomass expressed as kg of live weight is a good representation of the actual biomass of concern (i.e. microflora) over all species. Therefore, it should be considered a very rough estimate of the population at risk of being treated.¹¹²

Box 16 – Anatomical Therapeutic Chemical classification system for veterinary medicinal products (ATCvet)

The Anatomical Therapeutic Chemical classification system for veterinary medicinal products (ATCvet) classifies veterinary medicines based on the same overall principles as the ATC codes for substances used in human medicine (see Box 6 in section 3.3.1). The ATCvet codes enable the international exchange and comparison of data on drug use in veterinary medicine, but also the comparison of the human and veterinary use of medicines. Usually an ATCvet code is created by inserting a Q in front of an ATC code from the human ATC system (e.g. QJ01 refers to antimicrobial agents for systemic use). In some cases, specific ATCvet codes have been created.

All assigned ATCvet codes can be found in the complete ATCvet Index, which is issued annually. A searchable online ATCvet Index is available at https://www.whooc.no/atcvet/atcvet_index/.

Source: <https://www.whooc.no/atcvet/>¹¹⁵



4.1.2.2 Quality indicators for antibiotic use

As was said in section 4.1.1, the ECDC, the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) have jointly established a list of 15 harmonized outcome indicators to assist EU member states in assessing their progress in reducing the use of antimicrobials and antimicrobial resistance in both humans and food-producing animals. There are 4 primary indicators, monitoring essential points, and 11 secondary indicators, monitoring highly recommended points to assess progress made in member states' action plans. The indicators with regard to antibiotic use in food-producing animals are presented in Box 17.¹¹⁰

Box 17 – ECDC/EFSA/EMA outcome indicators for use of antibacterials for systemic use (ATC group J01) in the veterinary sector

Primary indicator:

Overall sales of veterinary antimicrobials (mg/PCU)

Secondary indicators:

Sales of 3rd- and 4th-generation cephalosporins (mg/PCU)

Sales of quinolones (mg/PCU), specifying the proportion of fluoroquinolones

Sales of polymyxins (mg/PCU)

Source: <https://ecdc.europa.eu/en/publications-data/ecdc-efsa-and-ema-joint-scientific-opinion-list-outcome-indicators-regards>¹¹⁰

Key messages

- In the international literature on human medicine, the use of antimicrobial/antibacterial agents has been expressed by many different measures, e.g. DDDs per 1000 inhabitants per day (DID), packages per 1000 inhabitants per day (PID), prescriptions per 1000 inhabitants per day (PrID), DDDs per 1000 patient days, DDDs per 1000 admissions. It is currently not clear yet which metric and indicator correlate(s) best with antibiotic-associated risks such as resistance pressure.

- Also in veterinary medicine, various measures are used to quantify antibiotic use, e.g. the mg/PCU, the DDD for Animals (DDDvet) per 1000 animals and per year, the Defined Course Dose for Animals (DCDvet) per 1000 animals and per year. The population at risk can be described in terms of biomass (or live weight) at risk of being treated.
- ECDC, the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) have jointly established a list of 15 harmonized outcome indicators to assist EU member states in assessing their progress in reducing the use of antimicrobials and antimicrobial resistance in both humans and food-producing animals.

4.2 How is antibiotic use monitored?

4.2.1 Human sector

This section describes how antibiotic use is monitored in Belgium and Europe. Likewise, antimicrobial resistance and healthcare associated infections are monitored at the Belgian and European level, but this was considered out of scope for the present report.

4.2.1.1 Monitoring of antibiotic use in Belgium

Several initiatives, at national as well as at local/hospital level, have been taken to analyse antibiotic use data and to provide feedback on prescription patterns to the prescribers. Here we only mention the national initiatives, which are – together with the initiatives at local/hospital level – further described in section 6.1.1 when feedback on antibiotic prescription is provided to prescribers, as an intervention to improve prudent antibiotic use.

In Belgium, the monitoring of the prescription and use of antibiotics is organised separately for the ambulatory and hospital sector.



AMBULATORY SECTOR

The database **Farmanet – Pharmanet** was created in 1996 to monitor the sale of pharmaceutical products reimbursed by the compulsory health insurance and delivered by the pharmacies open to the public.⁷⁸ Farmanet – Pharmanet does not contain data on non-reimbursed drugs, nor on drugs delivered by hospital pharmacies.⁵⁹

The Farmanet – Pharmanet data are also used by RIZIV – INAMI to provide feedback on prescription behaviour so that prescribers can compare their own prescription behaviour with peers (benchmarking). More specifically with regard to antibiotics, feedback reports are sent to general practitioners, grouped practices, and in some years to other medical specialists prescribing antibiotics in ambulatory care. Further details on these feedback reports and their impact are provided in the section 6.1.1.

The Farmanet – Pharmanet database is an important source of information for some RIZIV – INAMI publication series, such as Pharmaceutical key figures ('Farmaceutische kengetallen'/'Tableaux de bord pharmaceutiques'; every year the prescribing behaviour of MDs and dentists are described and recent evolutions explained) and the Statistics on the large groups of prescribers ('Statistieken over de grote groepen van voorschrijvers'/'Statistiques sur les grands groupes de prescripteurs'; statistics on the prescribing behaviour of large groups of doctors and dentists, classified according to different levels of detail), which are publicly available on the Farmanet – Pharmanet website (<https://www.riziv.fgov.be/nl/statistieken/geneesmiddel/Paginas/Statistieken-geneesmiddelen-apotheken-farmanet.aspx>). For scientific and/or educational purposes, data can also be requested.

HOSPITAL SECTOR

ABUH-project

In order to follow the antibiotic stewardship programmes, which were installed from July 2007 on in all acute hospitals and in large chronic care hospitals with at least 150 beds (see section 6.1.1), the ABUH project was launched. All hospitals receiving funding for antibiotic stewardship were obliged to report on a yearly basis about the use of antimicrobial drugs to

the then Scientific Institute of Public Health (WIV – ISP, since 2017 merged with CODA – CERVA into Sciensano).^{84, 116}

Data collection

A web-based data collection application, called NSIHweb, was developed which offered a standardized calculation methodology as well as a centralized recording system.¹¹⁶ Data on antibiotic use were extracted out of the hospital pharmacy routine invoicing system; the data were limited to inpatients (i.e. the emergency department, day care and ambulatory care were excluded). In order to establish a certain level of comparison between hospitals, hospitals were asked to forward also data on some hospital's activity characteristics (e.g. number of admissions, number of patient-days). No data on patient age or diagnosis were registered, nor any information related to the prescriber.¹¹⁶

The mandatory aspect of the surveillance concerned antimicrobial use in the entire hospital, the paediatric wards and the non-paediatric departments, including (among others) the intensive care units (ICU) as well as the haematology and/or oncology units (HAO). Because these two units are known to be places with highest antimicrobial use, hospitals could also provide, on a voluntary basis (given the high workload for that task), the use data of the ICUs and/or HAO.¹¹⁶

Coverage & feedback

Although the surveillance was compulsory, the participation rate was not 100%. For 2012 for instance, it was 88.2%. This may be due to technical or structural issues (re-organisations like the merging and/or moving of hospital sites, new computer environment, etc.), but even so some hospitals did not provide any data nor explanations for several consecutive years.

After data entry, hospitals could review the in-hospital antibiotic use trends (longitudinal analyses) as well as basic national comparative indicators (point analyses). Hospital data were stored on a secured server at the WIV – ISP and used to draw national antibiotic use trends over time.¹¹⁶



From ABUH to BeH-SAC

In 2013 the ABUH project was replaced by BeH-SAC, which stands for 'Belgian Hospitals-Surveillance of Antimicrobial Consumption'. From then on, data are no longer provided by the hospitals themselves, but transferred directly from RIZIV – INAMI to Sciensano. This approach offers several advantages: more detailed information (e.g. data per hospital department), more possibilities for analyses and benchmarking (per service, acute vs. chronic/psychiatric hospitals, per type of hospital (primary, secondary, tertiary), per size (number of beds); in addition the data collection did no longer imply an extra workload for the hospitals.¹¹⁷ Hospitals can receive feedback on antimicrobial use (incl. benchmarking) through the Healthstat platform of the Healthdata.be project (<https://www.healthstat.be>). In addition, since July 2018 reports with national data on antibiotic use in hospitals are made publicly available through the same website.

Critical notes

Since the feedback given by BeH-SAC is not on the service (ward) level but at a higher aggregated level (e.g. surgery or internal medicine), the data cannot be used for feedback purposes at the prescriber or ward level. The delay of the feedback (approximately 14 months) is another criticism heard in hospitals. (*Personal communication*)

But also, hospitals that do not perform well, are not forced to improve the situation. Hospitals do not get any advice on what policy improvements can be/should be realised. There is no control, no penalty if no improvement is realised. Last but not least, the general public is not aware which hospital performs well and which one not.¹¹⁸

4.2.1.2 Monitoring of antibiotic use in Europe

In the human sector, several European networks are devoted to the surveillance of antimicrobial use in ambulatory care, in hospitals and in long long-term care facilities. They are shortly described in the following paragraphs.

SURVEILLANCE OF ANTIMICROBIALS FOR SYSTEMIC USE IN THE AMBULATORY AND HOSPITAL SETTINGS – ESAC-NET

Since 2011, the European Centre for Disease Prevention and Control (ECDC) collects annually data from national statistics on the use of antimicrobials for systemic use in the ambulatory and hospital settings in EU and European Economic Area (EEA)/ European Free Trade Association (EFTA^x) countries; this surveillance network is called ESAC-Net (the European Surveillance of Antimicrobial Consumption Network).⁸⁵ ECDC has developed and validated protocols for quantitative measurement and qualitative description of antimicrobial use patterns, and has contributed to improve the use of antimicrobials in Europe.⁹ ESAC-Net was preceded by the European Surveillance of Antimicrobial Consumption (ESAC) project^y, an international network of national surveillance systems which collected antibiotic use data and was launched in 2001.

Data on the use of antimicrobials are collected at the product level and the ATC classification system (up to the fourth level, see Box 6) is used for the allocation of antimicrobials into groups. The data sources are national sales and reimbursement data, including information from national drug registers.⁸⁵

For Belgium the antibiotic use data (based on reimbursement data) are collected by the National Institute for Health and Disability Insurance (RIZIV – INAMI), and then transferred to and validated by Sciensano. In the validation phase, BAPCOC as well as the University of Antwerp (Laboratory of Medical Microbiology) are involved. Sciensano then uploads the data from

^x The EEA/EFTA States are Iceland, Liechtenstein and Norway.

^y The project was funded by the European Commission and headed by the University of Antwerp.¹¹⁹ The main objective of the ESAC project was to consolidate the continuous collection of comprehensive antibiotic use data,

for ambulatory care and hospitals, in all 34 participating European countries. The database was used to develop health indicators of antibiotic use and a set of core indicators was used to give feedback to the participating countries.¹²⁰



the national networks to a central database (The European Surveillance System - TESSy), maintained at ECDC. After uploading, each country approves its own data and the results are made available from the ECDC website in the week of the European Antibiotic Awareness Day (i.e. mid November) of the following year.⁸⁵

SURVEILLANCE OF ANTIMICROBIAL USE AND HEALTHCARE-ASSOCIATED INFECTIONS IN ACUTE CARE HOSPITALS – HAI-NET POINT PREVALENCE SURVEY

Data on the prevalence of antimicrobial use on one day ('one day survey') in patients admitted in European acute care hospitals are provided through the ECDC-coordinated point prevalence surveys (PPS, see Box 18) of antimicrobial use and healthcare-associated infections. The first EU-wide point prevalence survey (PPS) coordinated by ECDC was held in 2011 and 2012; a second was run in 2016-2017 (spread over four periods: April-June 2016, September-November 2016, April-June 2017, and September-November 2017).

Box 18 – Point prevalence surveys

A point prevalence survey is a count of the number of patients with a particular condition/treatment (in this case either a healthcare-associated infection or an antimicrobial agent) at a particular time (in this case a day), as a proportion of the total number of patients who are hospitalised at that particular time. A **point prevalence survey** only counts the condition/treatment if present at the time (on the day) of the survey, but does not count if it is present at other times during the patient stay in the hospital.⁸⁵

All participating countries use the same standardised protocol, which stipulates (among others) how a validated diagnosis, according to ECDC case definitions, should be performed.¹²¹ Ideally, the results should be based on data from hospitals that are representative of all acute care hospitals in the European Union and - to meet national objectives - results should also be representative for each of the Member States' total hospital population to be meaningful. Therefore, the protocol stipulates how the hospitals should be selected, but also the recommended sample size of patients and

hospitals by country.¹²¹ Data are collected at hospital level, but also at ward and patient level.

The Belgian national PPS coordination team of the 2016-17 PPS comprised collaborators from Sciensano, BAPCOC and the Federal Public Service Health, Food Chain and Environment (FOD VVVL – SPF SPSCAE). Hospitals receive €2.00 for each patient included in the database. (Sciensano, *personal communication*)

In March 2018, the participating hospitals received from ECDC a feedback report (in the shape of an excel sheet), with detailed information on their hospital and the national and regional data (benchmarking). (Sciensano, *personal communication*)

Critical notes

Consulted stakeholders (see chapter 7) argued that the ECDC PPS protocol is very heavy (demanding), requiring a lot of (staff) efforts, without clear benefits for the hospitals. In addition, hospitals cannot be forced to participate to the PPS. Moreover, if hospitals do not perform well, it is their responsibility to improve the situation.

SURVEILLANCE OF ANTIMICROBIAL USE AND RESISTANCE – GLOBAL POINT PREVALENCE SURVEY

The aim of the global point prevalence survey is to establish a global network for point prevalence surveys and aims to include as many hospitals from as many countries from all continents.^{122, 123} The first global-PPS in Belgium was organised in February-April 2015, the second in September-November 2017.

Its protocol is based on the original ESAC-PPS protocol (<http://www.global-pps.com>); it is less labour intensive than the ECDC-PPS protocol. Data collection implies conducting a 'one day survey' including all admitted inpatients at 8 o'clock receiving an antimicrobial treatment; the day care, recovery and emergency departments are excluded. After final data-entry and validation, each participating hospital can download a real-time feedback report which can be used for e.g. local communication (see further details in section 6.1.1).



Participation of hospitals and all fieldwork at the hospital level are done on a voluntary basis.¹²² The global PPS in Belgium is coordinated by BAPCOC; it is – at the global level – funded by bioMérieux.^{122, 123}

Critical notes

The sponsoring by bioMérieux is for some countries a reason not to participate. As participation is voluntary, the data at a national level should not be regarded as representative. Last but not least, according to some consulted stakeholders (see chapter 7) it may be confusing for hospitals that they are invited to participate in two different PPS.

SURVEILLANCE OF ANTIMICROBIAL USE AND HEALTHCARE-ASSOCIATED INFECTIONS IN EUROPEAN LONG-TERM CARE FACILITIES – HALT PROJECTS

Data on the prevalence of antimicrobial use in residents at long-term care facilities (incl. nursing homes) are collected by ECDC within the HALT projects. The first HALT data collection in EU/EEA Member States and in EU enlargement countries took place in May-September 2010, the second in April-May 2013 and the third in 2016-2017. Participating countries are encouraged to collect data in LTCFs that are representative for all LTCFs in the country/region, but given the large variety and number of LTCFs and the voluntary nature of the PPS, this is not always possible.¹²⁴ For Belgium, the coordination is performed by Sciensano (formerly WIV – ISP). In March 2018, the participating LTCFs received from ECDC a feedback report (in the shape of a pdf document), with the most important findings. (Sciensano, *personal communication*)

4.2.2 Veterinary sector

4.2.2.1 Monitoring and registration of antibiotic use in Belgium

SURVEILLANCE OF ANTIMICROBIAL USE IN FOOD-PRODUCING AND COMPANION ANIMALS

The Belgian Veterinary Surveillance of Antimicrobial Consumption (BelVet-Sac) database was originally (2007) a BAPCOC initiative in collaboration with the faculty of veterinary medicine of Ghent University and was further developed and financed by FAGG – AFMPS.¹²⁵ The data collection covers all veterinary antimicrobials sold to a veterinarian or pharmacist in Belgium and all antimicrobial premixes incorporated in medicated feed intended to be used in Belgium. It includes antibiotic use data for both food-producing and companion animals.

The data are provided by the 25 wholesale distributors who are registered for supplying veterinarians and pharmacies with veterinary medicines. The legislation stipulates that distributors have to keep record of all sales and have to forward these data to FAGG – AFMPS, which is the responsible Belgian authority.¹²⁶⁻¹²⁸ In addition, data on premixes containing antibiotics and Zinc Oxide^z are forwarded every year to FAGG – AFMPS by the 57 Belgian compound feed producers that are licensed to produce medicated feed.¹²⁸

All antibiotics used for veterinary medicine are covered by the BelVet-Sac data collection. In contrast to the ESVAC database, antibiotics for dermatological use and use in sensory organs are not excluded. Therefore, data presented in the BelVet-Sac report may partially differ from the data reported in the ESVAC report (see section 4.2.2.2).

In the BelVet-Sac reports, biomass (in kg) is calculated as 'the sum of the amount of beef, pork and poultry meat produced that year in Belgium plus

^z Zinc oxide (ZnO) is used to prevent post weaning diarrhoea in piglets. Zinc oxide (ZnO) is used to prevent post weaning diarrhoea in piglets. According to European legislation, Belgium is obliged to delete all authorizations of veterinary medicinal products based on ZnO for oral administration to food-

producing animals by 26 June 2022. This decision was taken upon the advice of the Committee for Medicinal Products for Veterinary Use, which concluded unanimously that the overall risk-benefit balance of veterinary medicines containing ZnO is negative.¹²⁹



the number of dairy cattle present in Belgium times their metabolic weight per head'.¹³⁰ It does not take other animal species such as horses, rabbits, small ruminants, nor companion animals (estimated to be 8% of the biomass present in Belgium) into account, while the data on antibiotic use also cover the use in these species. In the BelVet-Sac report the biomass also includes animals slaughtered in Belgium but raised in other countries, but it excludes animals raised in Belgium but slaughtered abroad.¹³⁰

BelVet-Sac data do not allow reporting at animal species level mainly because many antibiotic products are registered for use in different animal species and there are currently no data available on the proportions of products used in the different species. However, herd level based data collection systems like SANITEL-MED, AB register, BVK and BIGAME (cf. infra) allow reporting of use at animal species level.

The BelVet-Sac data are reported on a yearly basis on the website of FAGG – AFMPS. The most recent report was published in June 2018, reporting on 2017 data.¹³¹

SURVEILLANCE OF ANTIMICROBIAL USE IN FOOD-PRODUCING ANIMALS AND FEEDBACK TO FARMS

In the electronic database SANITEL-MED, coordinated and managed by FAGG – AFMPS, all prescribed, supplied and administered antibiotics used in food-producing animals are registered. The registration is mandatory since 27 February 2017 (in a first phase) for poultry, pigs and veal calves.¹³² Cattle farmers can join on their own initiative through the DQA (Dairy Quality Assurance) quality label, which has a coverage of about 90%.¹³³ Veterinarians register each antibiotic they prescribe and/or administer on farm level through an online-tool. The farmer however is also responsible for the data and must therefore validate (and if necessary refuse or correct) the data input of the veterinarian.

Based on the SANITEL-MED register, AMCRA produces twice a year feedback reports at farm level. Farms can also compare their own data with the national average, which may stimulate efforts to (further) rationalize

antibiotic use. Veterinarians can also extract a chronological overview for each farm, as well as an overview per product. Basically the SANITEL-MED register is installed as an instrument for self-regulation and adaptation, rather than for control by the authorities.

The first SANITEL-MED individual farm level benchmark reports were published for veal calves in June 2018 (in May 2019 the next report is expected), for broilers in November 2018 (in April 2019 the next report is expected) and for pigs in December 2018 (in March 2019 the next report is expected). (AMCRA, *personal communication*) The SANITEL-MED database is also used to produce national reports.

Mandatory registration at farm level

Farmers are obliged to have a document provided by the veterinarian to justify every medicine delivered or present at the farm, also in case the veterinarian himself treats the animals. This document is either the 'administration and provision document' ('toedienings- en verschaffingsdocument' (TVD) – 'document d'administration et de fourniture' (DAF)) or a copy of the veterinary prescription.⁵⁷ The farmer keeps a 'register IN' (consisting mainly of the received TVD – DAF documents & prescriptions) and a register OUT (listing the administered antibiotics by himself out of his stock). The register IN justifies the presence of veterinary medicines, while the register OUT justifies their use. The Royal Decree of 21 July 2016 defines the conditions for medication use by veterinarians and farmers.

When there is a guidance contract (see section 3.2.2), the farmer has to register all treatments he performs himself in the register OUT, except treatments of non-weaned piglets and calves younger than four weeks born at the farm (for products with withdrawal times < 1 month). When there is no guidance contract, the farmer does not have to mention a treatment in the register OUT^{aa}, but just needs to follow the instructions as described in the TVD – DAF documents or the prescription which is filed in the register IN.^{125,}

¹³⁴

^{aa} Except if the treatment starts at a later date than the date of the TVD – DAF or prescription.



Certification by label schemes and quality control in animal production

The use of antibiotics in food-producing animals and its registration have become important quality criteria. Indeed, the **sale and export of meat** have been proven to be **powerful leverages** in the food-producing sector to use antibiotics more prudently. For that purpose several initiatives have been taken in recent years.

In 2014, the **AB register** ('AB register' – 'Registre AB', www.abregister.be) has been launched by the non-profit organization BelPork, which is the owner of the Certus quality assurance system for pig meat. This private data-collection system aims at mapping the antibiotic prescription and use among producers of pig meat. All antibiotics used, including the use of premixes supplemented with antibiotic and the use of zinc oxide^z, must be registered in the AB register. One of the important driving forces for the establishment of the AB register was the sale of pork in Germany, which was only possible through a collaboration with the German Quality system Q&S^{bb}.

Belgian producers certified by one of the participating quality labels (i.e. Certus, CodiplanPlus Varken and Colruyt), are obliged to register their antibiotic use as one of the quality criteria. Since 2016, the mandatory registration has been enlarged to poultry producers who are certified by BelPlume.¹³⁵ Since 1 October 2018 also dairy farming ('Integrale Kwaliteitszorg Melk' (IKM) – 'Qualité Filière Lait' (QFL)) has joined.¹³⁵ Producers who are not certified by one of those labels, can join on a voluntary basis.

AMCRA has individual contracts with the quality labels who want to provide their farmers with information complementary to what they already receive through Sanitel-Med. The AB register reports for pigs and poultry are sent out at a higher frequency. For pigs, for instance, reports are sent every 3 months (in March 2019 the next report is expected). Further efforts are made to reduce the delay between the introduction of the data and the development of the reports. (AMCRA, *personal communication*) If antibiotic use is too high (i.e. a farm is among the 10% highest users), the farmer and

his veterinarian are expected to take measures, which are then followed-up by the label schemes themselves.

In the period 2014-2016, 2 117 Belgian pig farms have reported data to the AB register. Over that period, the antibiotic use in these farms decreased with 14% taking all (pig) age groups together.¹³⁶

The professional union for veal calf farmers ('Beroepsvereniging voor de Belgische Kalfsvleessector' – 'Fédération de la filière de veau Belge') has set up a proper quality programme, called BCV (Belgian Controlled Veal), in 1996. Since the start, the execution (audits, samples, etc.) of the BCV specifications has been outsourced to the independent control and certification body SGS (www.sgs.com). Since 2017, the subject of prudent antibiotic use has also been included in the BCV specifications, hence the database **SGS-BCV veal calves** contains the data on deliveries/prescriptions of antibiotics delivered on participating veal calf farms. (Beroepsvereniging voor de Belgische Kalfsvleessector, *personal communication*) Input is done by the veterinarian, per batch of animals set-up. Per quarter, the results of all batches from a certain production type that have finished off in that quarter are compared. Thresholds are set on the 90th percentile of the distribution of all batches in a quarter; farmers that are above the 90th percentile threshold are considered 'high users'. Farmers receive the benchmarking results of their respective batches; high users are expected to reduce their use of antibiotics.¹³⁷

In the Walloon region there is the initiative **Base Informatique de Gestion des Antibiotiques et des Médicaments en Elevage (BIGAME)**, which is comparable to the AB Register. It has been developed in cooperation with the farmers' and veterinarians' union (respectively Fédération Wallonne de l'Agriculture and Union Professionnelle Vétérinaire). BIGAME covers pig, poultry, dairy, and veal calf producers and participation is voluntary.¹³⁸

In order to avoid double registration for the veterinarians (in different databases), the data registered in the AB register, SGS-BVK database and BIGAME are transmitted four times each year to SANITEL-MED, the

^{bb} Q&S is the abbreviation of Qualität & Sicherheit (Quality and safety); it is the German quality monitoring system for food. (www.q-s.de)



national data collection system (cf. supra), which is mandatory for pig, poultry and veal calf producers.¹³³

4.2.2.2 *Monitoring and registration of antibiotic use at the European level*

SURVEILLANCE OF VETERINARY ANTIMICROBIAL USE - ESVAC

The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project was launched by the European Medicines Agency (EMA) in September 2009 following a request from the European Commission to develop a harmonized approach to the collection and reporting of data on the veterinary use of antimicrobial agents in all member states.¹³⁹ The main indicator to express the sales of antimicrobials is milligrams of active ingredient sold per population correction unit^b (mg/PCU, see Box 15).

For the most recent report (2018, covering the period 2011-2016), 29 EU/EEA countries and Switzerland submitted data on sales (28 countries) or prescriptions (two countries) of antimicrobial veterinary medicinal products (VMPs) to the European Medicines Agency for 2016. For Belgium BelVet-Sac data are forwarded to ESVAC by FAGG – AFMPS.

Key messages

- **In the ambulatory sector, the monitoring of antibiotics can be done through the database Farmanet – Pharmanet, created by RIZIV – INAMI. The dataset is used to send feedback reports to individual prescribers.**
- **Sciensano monitors the prescription and use of antibiotics in the hospital sector through BeH-SAC (Belgian Hospitals - Surveillance of Antimicrobial Consumption). Hospitals can receive feedback on antimicrobial use (incl. benchmarking) through the Healthstat platform of the Healthdata.be project and since July 2018 reports with national data on antibiotic use in hospitals are made publicly available on the same website.**
- **At the European level, ECDC monitors antibiotic use through annual data collections (i.e. ESAC-Net, for the ambulatory and**

hospital sector) and point prevalence studies in hospitals (i.e. HAI-Net) and long-term care facilities (i.e. HALT).

- **FAGG – AFMPS monitors antibiotic use through BelVet-SAC (food-producing and companion animals) and SANITEL-MED (only food-producing animals). The BelVet-Sac data are reported on a yearly basis on the website of FAGG – AFMPS. SANITEL-MED data are used to provide farms with individual feedback reports (incl. benchmarking).**
- **In the food-producing sector, the sale and export of meat have been proven to be powerful leverages to use antibiotics more prudently. For that purpose several initiatives have been taken in recent years (e.g. certification by label schemes and quality control).**
- **At the European level, the European Medicines Agency (EMA) monitors antibiotic use through the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project.**

4.3 Data on antibiotic use in Belgium, in a European context

In the following paragraphs the use of antibiotics in the Belgian ambulatory, hospital, nursing home and veterinary sectors is presented in a European context. The data are particularly derived from the most recent ESAC-Net, HAI-Net, HALT and ESVAC reports and publications.^{8, 39, 109, 140-144} In addition, information on self-medication with antibiotics, reasons for taking antibiotics and knowledge on antibiotics were retrieved from the most recent Eurobarometer survey.⁵³ In section 4.4 the Belgian data on the ambulatory and hospital sector are further explored, mostly based on data provided by RIZIV – INAMI.

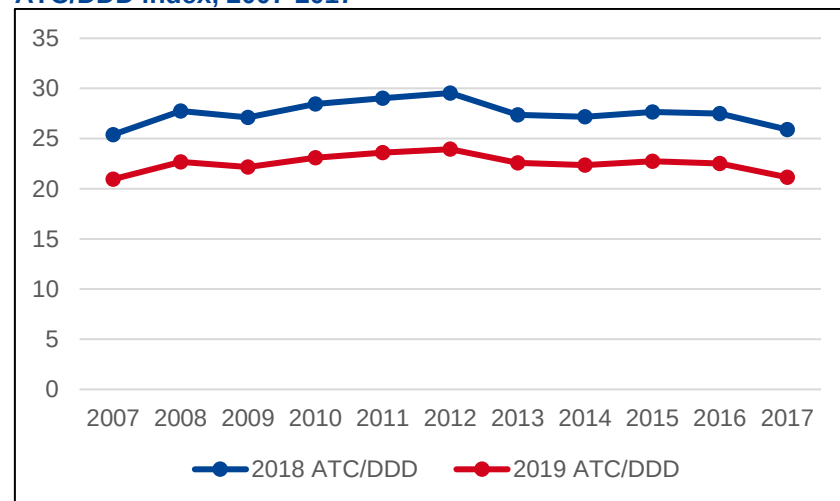
4.3.1 Human sector

The data presented in this chapter are based on the data available from the ECDC interactive website <https://ecdc.europa.eu/en/antimicrobial-consumption/database/country-overview> (last access: 29 January 2019).¹⁰⁹ The data were analysed applying the ATC Index with DDDs 2019.¹⁴⁵ The DDDs 2019 better reflect the doses used in clinical practice than those listed in the ATC Index with DDDs 2018.⁸ The new DDD allocation requires more



grams of antimicrobials to compose one DDD; the update includes substantial alterations in DDDs for eight antibacterials^{cc}. The application of the new DDDs has the largest impact on penicillin use data.⁸ The antimicrobial use figures from previous years expressed in DDD per 1000 inhabitants per day are lower when the new 2019 ATC/DDD index is applied compared to the figures published in 2018 (see Figure 7). As a consequence, the data are lower than what is presented in the ECDC Annual Epidemiological Report for 2017 - Antimicrobial consumption, as in that report the data were analysed based on the DDDs listed in the ATC Index for 2018.^{8, 146}

Figure 7 – Trends in the use of antibacterials for systemic use (ATC group J01), expressed with the 2018 ATC/DDD index and the 2019 ATC/DDD index, 2007-2017



Source: ECDC, personal communication

^{cc} Alterations resulting from the update of the ATC Index with DDDs 2019: ampicillin from 2g to 6g, oral amoxicillin from 1g to 1.5g, parenteral amoxicillin

4.3.1.1 Antibiotic use in the ambulatory sector

ANTIBIOTIC USE IN 2017

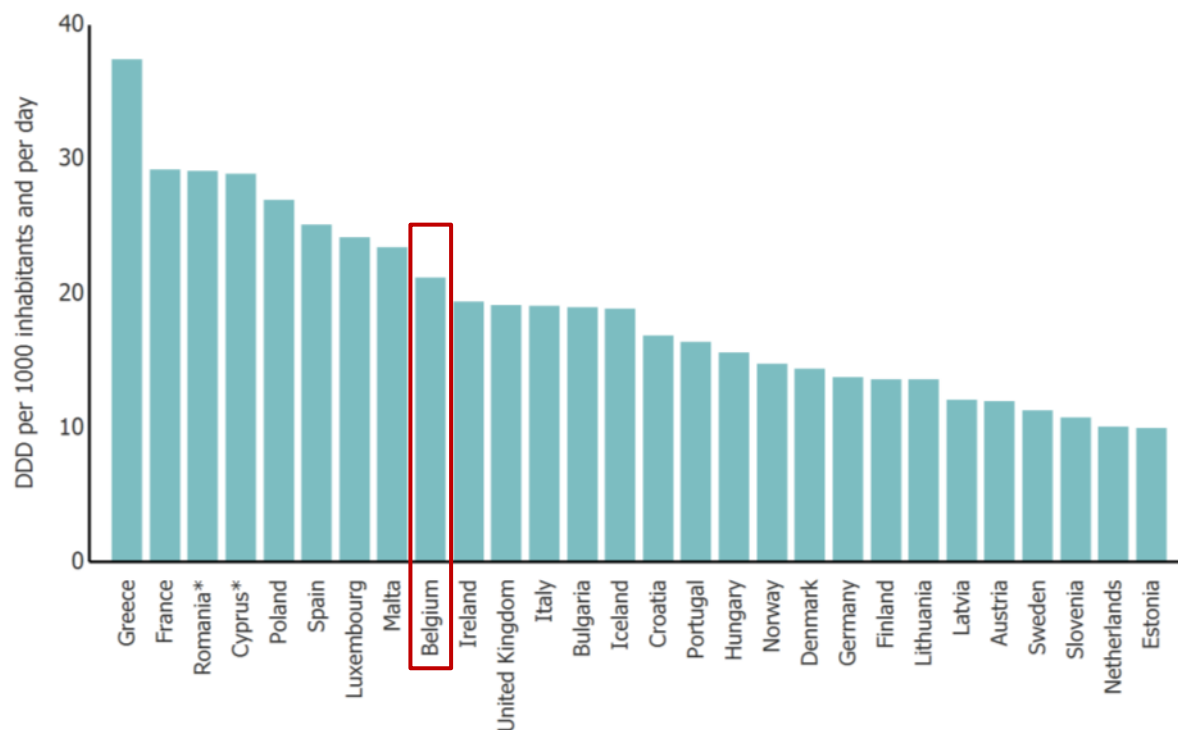
In 2017, the total use of antibiotics for systemic use in the Belgian ambulatory sector equalled **21.1 DID** (Defined Daily Doses (DDD) per 1000 inhabitants per day or DID), which is higher than the EU/EEA population-weighted mean of 18.4 DID.^{8, 109} Among the 28 countries that transferred data to the European Centre for Disease Prevention and Control (ECDC), Belgium was in the **top 9 highest** antibiotic prescribers (Figure 8).⁸

When these data are expressed as packages of antibiotics for oral use, Belgium ranked with **1.89 packages per 1000 inhabitants per day (PID)** 11th of the 17 countries that submitted these data. The EU/EEA population-weighted mean was 3.06 packages per 1000 inhabitants per day and ranged from 0.95 in Sweden to 4.53 in France.⁸

from 1g to 3g, oral amoxicillin with beta-lactamase inhibitor from 1g to 1.5g, cefepime from 2g to 4.5g, meropenem from 2g to 3g, parenteral ciprofloxacin from 0.5g to 0.8g and parenteral colistin from 3g to 9g.



Figure 8 – Use of antibiotics (ATC group J01) in the ambulatory sector in Europe, 2017



*: Cyprus and Romania provided total care data (i.e. including the hospital sector)^{dd}

Source: European Centre for Disease Prevention and Control, ESAC-Net interactive website, 2019¹⁰⁹

^{dd} The total care data from Cyprus and Romania (i.e. including both the ambulatory and the hospital sector) are presented together with ambulatory use data from other countries, because on average, 90% of the total antibiotic use data refer to use in the ambulatory sector.

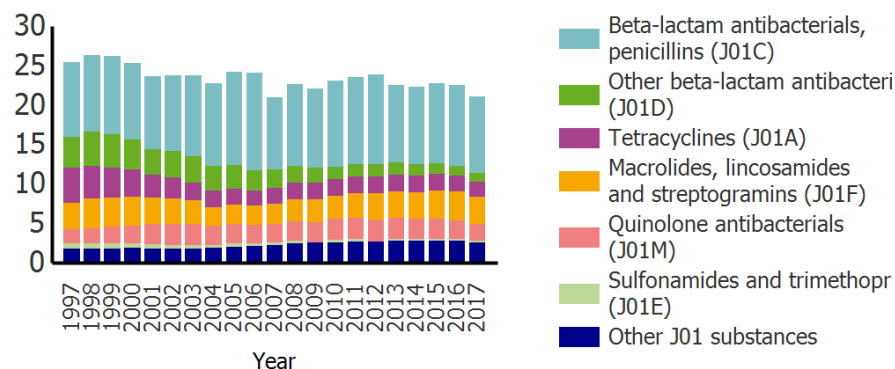


TRENDS IN TOTAL ANTIBIOTIC USE OVER TIME

Between 2007 and 2012, the total use of antibiotics in the ambulatory sector in Belgium expressed as DID fluctuated, increased and decreased again in 2013-2017 (Figure 9).¹⁰⁹

Note: due to a bug in the TESSy data, the data for the period 1997-2006 are presented based on the 2018 ATC/DDD index; at the moment of the editing of this report ECDC was still working on a solution. (ECDC, *personal communication*)

Figure 9 – Trend in the use of antibiotics for systemic use (ATC group J01) in the Belgian ambulatory sector expressed as DDD per 1000 inhabitants per day, 1997-2017



Source: European Centre for Disease Prevention and Control, ESAC-Net interactive website, 2019¹⁰⁹

QUALITY INDICATORS FOR ANTIBIOTIC USE IN THE AMBULATORY SECTOR

Unlike the ECDC Annual Epidemiological Report for 2017, no quartiles are provided to situate the Belgian data in a European context. Hence, we can only compare them to the EU/EEA minima and maxima (Table 4).

With regard to relative use (i.e. proportion of the total use of antibacterials for systemic use in the ambulatory sector), Belgian 2017 data are equal to the EU/EEA minimal data for β -lactamase sensitive penicillins and 3rd & 4th generation cephalosporins. Only 16 countries provided data on seasonal variation: Belgium is situated above the EU/EEA minimum and below the maximum.¹⁰⁹



Table 4 – Drug-specific quality indicators for outpatient antibiotic use in Europe, results for Belgium in 2017

Description	Abbreviation	Belgium	EU/EEA minimum*	EU/EEA maximum*
Use				
Use of antibacterials for systemic use (J01) expressed in DID	[J01_DID]	21.1	9.94	37.4
Use of penicillins (J01C) expressed in DID	[J01C_DID]	9.7	3.47	19.2
Use of cephalosporins (J01D) expressed in DID	[J01D_DID]	1.2	<0.1	7.7
Use of MLS, i.e. macrolides, lincosamides and streptogramins (J01F) expressed in DID	[J01F_DID]	3.4	0.5	7.0
Use of quinolones (J01M) expressed in DID	[J01M_DID]	2.2	0.4	6.2
Relative use				
Use of β -lactamase sensitive penicillins (J01CE) expressed as percentage ^{\$}	[J01CE_%]	<0.1%	<0.1%	28.0%
Use of combination of penicillins, incl. β -lactamase inhibitor (J01CR) expressed as percentage ^{\$}	[J01CR_%]	22.4%	0.1%	43.1%
Use of 3rd & 4th generation cephalosporins (J01(DD+DE)) expressed as percentage	[J01DD+DE_%]	<0.1%	<0.1%	8.8%
Use of fluoroquinolones (J01MA) expressed as percentage ^{\$}	[J01MA_%]	10.3%	2.4%	15.4%
Seasonal variation				
Seasonal variation** of the total antibiotic use (J01)	[J01_SV_%]	31.9%	12.2%	58.1%
Seasonal variation** of quinolone use (J01M)	[J01M_SV_%]	23.6%	1.1%	47.0%

*: No EU/EEA (population-weighted) mean/median available from the ESAC-Net interactive website, hence minimum/maximum (i.e. EU/EEA country with lowest c.q. highest result) provided to situate Belgian data; DID: Defined Daily Doses (DDD) per 1000 inhabitants per day; **: Over use in the winter quarters (October-December & January-March) compared to the summer quarters (July-September & April-June) of a one year period starting in July and ending the next calendar year in June, expressed as percentage: $[DDD(winter\ quarters)/DDD(summer\ quarters)-1] * 100$.

Source: European Centre for Disease Prevention and Control, ESAC-Net interactive website, 2019¹⁰⁹



4.3.1.2 Antibiotic use in the hospital sector

The data presented in this section are primarily based on the ECDC 'Annual Epidemiological Report for 2017 - Antimicrobial consumption' (ESAC-Net),⁸ and the ECDC 2016-2017 Point Prevalence Survey (PPS) of healthcare-associated infections and antimicrobial use in acute care hospitals.^{39, 140} In total, 11 800 patients who were admitted in 33 Belgian acute care hospitals^{ee}, were included in the ECDC PPS 2016-2017^{ff} (Table 5).¹⁴⁰

ANTIBIOTIC USE IN 2017

In 2017, the total use of antibiotics for systemic use in the Belgian hospital sector was **1.64 DID**, just below the EU/EEA population-weighted mean of 1.8. When the 23 countries which transferred data to ESAC-Net were ranked from lowest to highest users, Belgium ranked **9th** (Figure 10).^{8, 109}

Box 19 – Note with regard to antimicrobial use data in the Belgian hospital sector transferred to ESAC-Net

Due to the delay of reimbursement data in Belgian hospitals and corrections that can occur until two years after the actual use, the antimicrobial use in hospitals has been underestimated in the previous years (starting from 2012) by approximately 15%. This underestimation has been corrected in Tessy, the central database of the European Surveillance System (maintained at ECDC) for the years 2012-2016 (<https://ecdc.europa.eu/en/antimicrobial-consumption/database/country-overview>). For 2017, ECDC made an estimation of the hospital use by extrapolating the current reimbursement data with +15%.¹⁰⁹

Table 5 – Prevalence of antimicrobial use in hospitals in Belgium and the EU/EEA, 2016-2017 ECDC PPS

	Number of eligible patients	Number of patients with at least 1 antimicrobial*	Observed prevalence (%; 95% CI)	Number of antimicrobials* prescribed	Number of antibacterials (J01) prescribed (proportion of all antimicrobials)	DDD per 100 patients
Belgium	11 800	3 320	28.1 (27.3-29.0)	4 103	3 842 (93.6%)	45.5
EU/EEA	310 755	102 093	30.5 (29.2-31.9)	139 609	128 881 (92.3%)	46.0

Antimicrobial:* Antimicrobial agents for systemic use within ATC groups A07AA (intestinal anti-infectives), D01BA (dermatological antifungals for systemic use), J01 (antibacterials for systemic use), J02 (antimycotics for systemic use), J04 (antimycobacterials) as second-line treatment of e.g. methicillin-resistant *Staphylococcus aureus* (MRSA) infections (rifampicin) or for treatment of mycobacteria other than tuberculosis (MOTT) and P01AB (nitroimidazole-derived antiprotozoals) were included. Antiviral agents and antimicrobials for the treatment of mycobacteria were not included; EU/EEA: 28 European Union/European Economic Area countries (Denmark, Lichtenstein and Sweden did not participate). For the calculation of the EU/EEA prevalence of antimicrobial use, the participating countries' prevalence was weighted using the number of occupied beds per day as estimated by the latest available Eurostat data.

CI: Confidence Interval

Source: Vandael et al., 2018¹⁴⁰; Plachouras et al., 2018³⁹

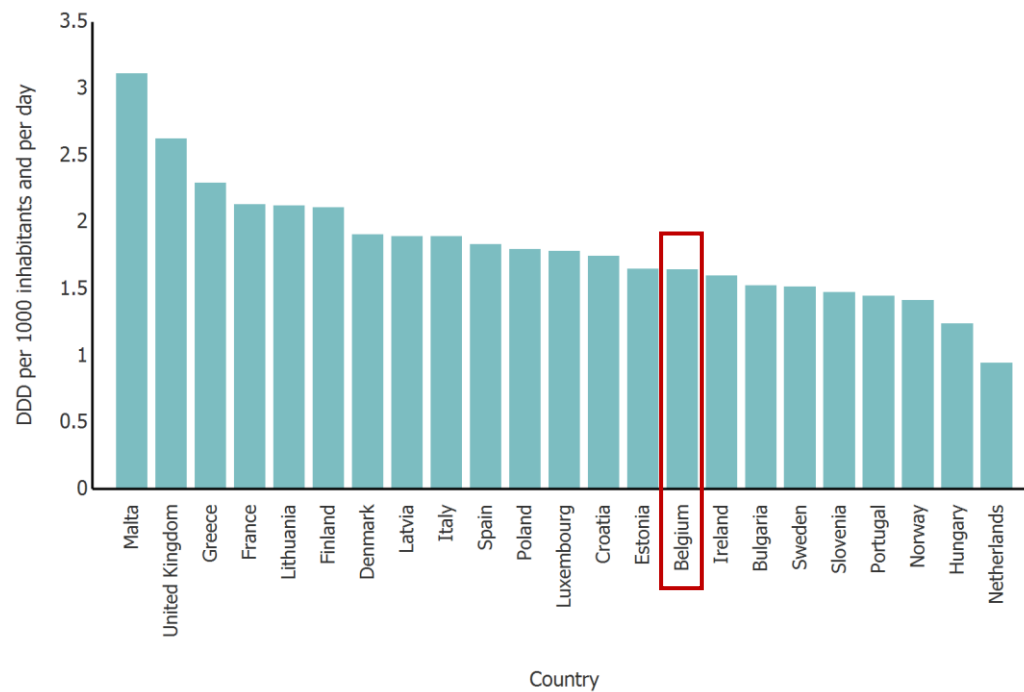
^{ee} Among the 33 acute care hospitals, 22 were primary hospitals, 9 secondary and 3 tertiary. In 2017 there were 102 acute care hospitals in Belgium. Patients who were admitted in day care (e.g. dialysis, oncological therapies),

day surgery or in the emergency room, were excluded, just like patients at outpatient departments.¹⁴⁰

^{ff} In Belgium, the surveys were performed between September and November 2017.¹⁴⁰



Figure 10 – The use of antibiotics in the hospital sector by antibiotic group, EU/EEA countries, 2017, expressed as DDD per 1000 inhabitants and per day



Note: The hospital sector data for Finland include use in remote primary health care centres and nursing homes, thus overestimating hospital use and underestimating use in the ambulatory sector compared to the other countries that report data from these sources as use in the ambulatory sector.

Source: European Centre for Disease Prevention and Control, ESAC-Net interactive website, 2019¹⁰⁹

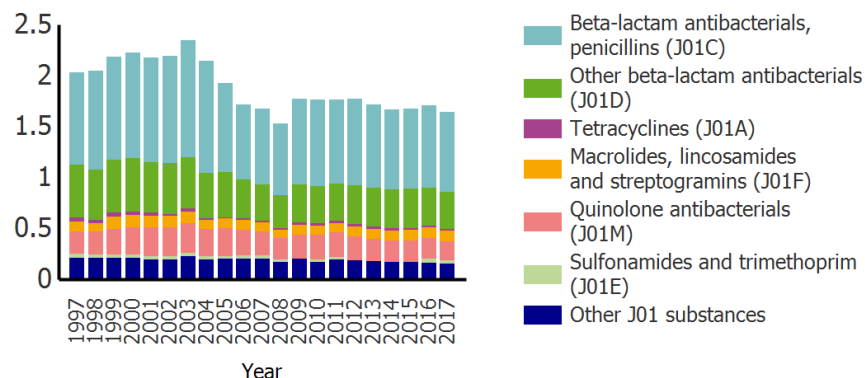


TRENDS IN TOTAL ANTIBIOTIC USE OVER TIME

From 2007 to 2008, the total use of antibiotics in the Belgian hospital sector expressed as DID increased, stayed stable for four years and fluctuated thereafter a little.¹⁰⁹

Note: due to a bug in the TESSy data, the data for the period 1997-2006 are presented based on the 2018 ATC/DDD index; at the moment of the editing of this report ECDC was still working on a solution. (ECDC, *personal communication*)

Figure 11 – Trend in the use of antibiotics (ATC group J01) in the Belgian hospital sector expressed as DDD per 1000 inhabitants per day, 1997-2017



Source: European Centre for Disease Prevention and Control, ESAC-Net interactive website (Accessed on 4 December 2018; data submitted to TESSy, The European Surveillance System)¹⁰⁹

PREVALENCE OF ANTIMICROBIAL USE IN HOSPITALS IN 2016-2017

The ECDC PPS revealed that on the day of the survey, 3 320 patients admitted in Belgian hospitals (i.e. 28.1% of all included patients) received at least one antimicrobial agent; 20.2% of the patients were prescribed more than one antimicrobial (Table 5). These proportions are somewhat lower than what was recorded at the EU/EEA level (32.9% and 29.4%, respectively). Antibacterials for systemic use (J01) accounted for 93.6% and 92.3% of all recorded prescriptions in Belgium and in the EU/EEA, respectively. In the majority of cases (65.6% in Belgium and 72.8% in EU/EEA) antimicrobials were administered parenterally, followed by oral intake (34.0% and 26.9%, respectively), inhalation (both 0.2%) and other routes (0.2% and 0.1%, respectively).^{39, 140}

INDICATIONS FOR ANTIMICROBIAL USE

In Belgium, the reason for antimicrobial use was documented in the patient's medical record for 80.8% of all antimicrobials, which is comparable to EU/EEA results (i.e., 80.2%).^{39, 140} About half of all antimicrobials were prescribed for a community-acquired infection (51.4% in Belgium and 49.5% in EU/EEA, see Table 6).

The proportion of antimicrobials prescribed for an acute hospital-acquired infection was higher in Belgium than in the EU/EEA (24.2% and 19.6%, respectively). In Belgium, the duration of surgical prophylaxis was in 43.8% one dose, in 32.4% one day and in 23.9% more than 1 day, which is better than at the EU/EEA level where 54.2% of surgical prophylaxis courses were prescribed for more than 1 day.^{39, 140}



Table 6 – Indications for antimicrobial use in Belgium and the EU/EEA, 2016-2017 ECDC PPS

	Total number of antimicrobials* prescribed	Treatment of infection (proportion**)			Prophylaxis (proportion**)		Other indication	Unknown
		Community-acquired infection	Acute hospital-acquired infection	Infection acquired in a LTCF or chronic-care hospital	Surgical prophylaxis	Medical prophylaxis		
Belgium	4 103	51.4%	24.2%	3.1%	13.5%	6.2%	0.9%	0.7%
EU/EEA	139 609	49.5%	19.6%	1.9%	14.2%	10.7%	NR	NR

Antimicrobial: Antimicrobial agents for systemic use within ATC groups A07AA (intestinal anti-infectives), D01BA (dermatological antifungals for systemic use), J01 (antibacterials for systemic use), J02 (antimycotics for systemic use), J04 (antimycobacterials) as second-line treatment of e.g. methicillin-resistant *Staphylococcus aureus* (MRSA) infections (rifampicin) or for treatment of mycobacteria other than tuberculosis (MOTT) and P01AB (nitroimidazole-derived antiprotozoals) were included. Antiviral agents and antimicrobials for the treatment of mycobacteria were not included; proportion**: proportion of total number of antimicrobials prescribed; EU/EEA: 28 European Union/European Economic Area countries (Denmark, Lichtenstein and Sweden did not participate). For the calculation of the EU/EEA prevalence of antimicrobial use, the participating countries' prevalence was weighted using the number of occupied beds per day as estimated by the latest available Eurostat data; LTCF: long-term care facility; NR: not reported.*

Source: Vandael et al., 2018¹⁴⁰; Plachouras et al., 2018³⁹

MOST COMMONLY USED ANTIBIOTICS BY INDICATION

In Belgium, combinations of penicillins, incl. beta-lactamase inhibitors (J01CR) are the most frequently prescribed antimicrobials in case of either community-acquired infections, hospital-acquired infections or infections acquired in a LTCF or chronic-care hospital (Table 7). For hospital-acquired infections, combinations of penicillins, incl. beta-lactamase inhibitors (J01CR) and fluoroquinolones (J01MA) are more often prescribed in Belgium than in the EU/EEA (25.1% vs. 19.8% and 13.0% vs. 9.4%), while the use of carbapenems in these situations is lower (6.7% vs. 9.9%).^{39, 140}

According to the guidelines, first-generation cephalosporins (J01DB, among which cefazolin) are given as surgical prophylaxis to 70.5% of the patients in Belgium; the EU/EEA average is only 26.6%.^{39, 140}

Table 7 – Most commonly used antimicrobials by indication in Belgium and the EU/EEA, 2016-2017 ECDC PPS

	Belgium	EU/EEA
Community-acquired infection		
Combinations of penicillins, incl. beta-lactamase inhibitors (J01CR)	36.0%	23.2%
Third-generation cephalosporins (J01DD)	8.7%	11.7%
Fluoroquinolones (J01MA)	12.2%	11.1%
Hospital-acquired infection		
Combinations of penicillins, incl. beta-lactamase inhibitors (J01CR)	25.1%	19.8%
Fluoroquinolones (J01MA)	13.0%	9.4%
Carbapenems (J01DH)	6.7%	9.9%
Infection acquired in a LTCF or chronic-care hospital		
Combinations of penicillins, incl. beta-lactamase inhibitors (J01CR)	34.1%	NR
Fluoroquinolones (J01MA)	15.5%	NR
Surgical prophylaxis		
First-generation cephalosporins (J01DB)	70.5%	26.6%
Combinations of penicillins, incl. beta-lactamase inhibitors (J01CR)	7.8%	15.1%
Second-generation cephalosporins (J01DC)	5.6%	17.9%
Medical prophylaxis		
Combinations of sulfonamides and trimethoprim (J01EE)	20.3%	NR
Combinations of penicillins, incl. beta-lactamase inhibitors (J01CR)	12.1%	NR

EU/EEA: 28 European Union/European Economic Area countries (Denmark, Lichtenstein and Sweden did not participate). For the calculation of the EU/EEA prevalence of antimicrobial use, the participating countries' prevalence was weighted using the number of occupied beds per day as estimated by the latest available Eurostat data; LTCF: long-term care facility; NR: not reported.

Source: Vandael et al., 2018¹⁴⁰; Plachouras et al., 2018³⁹

SITE OF INFECTION FOR WHICH ANTIMICROBIAL TREATMENT IS INDICATED

The most common site of infection was the respiratory tract (31.4%), followed by the urinary tract (16.2%), systemic infections (including laboratory-confirmed bacteraemia, 14.3%), and the gastrointestinal tract (13.6%)(Table 8). Other body sites accounted for 24.5% of the site of infection for antimicrobial treatment.¹⁴⁰ The Belgian data are very comparable to the EU/EEA average.³⁹

CHANGE OF ANTIMICROBIAL AGENT

In Belgium, a change in the antimicrobial treatment during admission was registered for 24.7% of all prescribed antimicrobials. More precisely, escalation, de-escalation and switch from intravenous to oral were recorded in 10.4%, 5.8% and 6.2% of cases. The respective proportions at EU/EEA level were 10.9%, 3.9%, and 4.0%, but they were solely based on the 76.8% of antimicrobial prescriptions for which this information was available. These changes were due to an adverse effect (0.5% in Belgium and 0.4% in EU/EEA) and change for another of unknown reason (both 1.8%).^{39, 140}

**Table 8 – Site of infection for which antimicrobial treatment is indicated in Belgium and the EU/EEA, 2016-2017 ECDC PPS**

	Number of antimicrobials* prescribed for infection (CAI, HAI, LAI)	Respiratory tract (proportion**)	Systemic infections (proportion**)	Urinary tract infections (proportion**)	Gastrointestinal tract infections (proportion**)	Other infections (proportion**)
Belgium	3 228	31.4%	14.3%	16.2%	13.6%	24.5%
EU/EEA	98 986	31.8%	14.7%	13.9%	13.6%	26.0%

Antimicrobial:* Antimicrobial agents for systemic use within ATC groups A07AA (intestinal anti-infectives), D01BA (dermatological antifungals for systemic use), J01 (antibacterials for systemic use), J02 (antimycotics for systemic use), J04 (antimycobacterials) as second-line treatment of e.g. methicillin-resistant *Staphylococcus aureus* (MRSA) infections (rifampicin) or for treatment of mycobacteria other than tuberculosis (MOTT) and P01AB (nitroimidazole-derived antiprotozoals) were included. Antiviral agents and antimicrobials for the treatment of mycobacteria were not included; CAI: Community-acquired infection; HAI: Hospital-acquired infection; LAI: Infection acquired in a LTCF or chronic-care hospital; proportion**: number of antimicrobial prescriptions for a specific infection site divided by the total number of antimicrobial prescriptions; EU/EEA: 28 European Union/European Economic Area countries (Denmark, Lichtenstein and Sweden did not participate). For the calculation of the EU/EEA prevalence of antimicrobial use, the participating countries' prevalence was weighted using the number of occupied beds per day as estimated by the latest available Eurostat data; LTCF: long-term care facility; NR: not reported.

Source: Vandael et al., 2018¹⁴⁰; Plachouras et al., 2018³⁹

4.3.1.3 Antibiotic use in nursing homes

The data presented in this section are based on the third ECDC Point Prevalence Survey (PPS) of healthcare-associated infections and antimicrobial use in European long-term care facilities (HALT-3), more precisely on the Belgian report prepared by Sciensano and an international publication in Eurosurveillance 2018.^{144, 143} As the results presented in these sources are limited to data from general nursing homes (providing principally care to seniors with severe illnesses or injuries), residential homes (facilities usually providing personal care, housekeeping and three meals a day) and mixed LTCFs (providing mixed services for elderly or other resident populations), so are the results presented in this section. Hence, throughout this section the term long-term care facility (LTCF) which is used in both publications, can be read as 'nursing home' (NH). HALT-3 was held in the period 2016-2017; in Belgium, the surveys were performed between September and November 2016.¹⁴⁴

For countries contributing to the survey with more residents than in the calculated recommended sample size, a randomised sub-sample was selected for the international publication.¹⁴³ That explains why in the Belgian

report data on 16 215 elderly residing in 158 nursing homes are reported, while in the international publication the respective Belgian numbers are 8 206 and 79 (Table 9).^{144, 143} The authors of the Belgian report note that given the fact that participation was voluntary, the reported data should not be considered representative for Belgium. But since the European publication did not provide detailed Belgian information, we had to rely for some results on the Belgian Sciensano report.

In this section only data on antimicrobial use are reported; healthcare-associated infections were considered out of scope for this report.

PREVALENCE OF ANTIMICROBIAL USE IN NURSING HOMES IN 2016-2017

On the day of the survey, 482 residents of Belgian nursing homes received at least one antimicrobial agent, resulting in an observed prevalence of antimicrobial use of 5.9% (95% CI 5.4-6.4), which was higher than the EU/EEA crude, pooled prevalence of 4.9% (95% CI 4.8-5.1, Table 9). The mean antimicrobial use prevalence of nursing homes was 5.8% (the same as at the EU/EEA level), but the median of 5.1% was higher than the EU/EEA median of 3.6%.¹⁴³

According to the Belgian report (based on 158 nursing homes), antimicrobials were predominantly administered orally (98.1%, while 88.1% at the EU/EEA level); the parenteral route was used for 1.5% of prescribed antimicrobials (while this proportion was as high as 10.9% at the EU/EEA level) and another route of administration (e.g. nasal or rectal) was reported for only 0.4% of prescribed antimicrobials (0.7% at the EU/EEA level).^{143, 144} Based on the Belgian report, antimicrobials were most frequently prescribed

within the same nursing home (83.5%), followed by an acute care hospital (8.7%) or another location (2.7%), with no data provided for the remaining 5.1%.¹⁴⁴ The respective proportions at the EU/EEA level were 77.9%, 12.9%, 5.1% and 4.2%.¹⁴³

Table 9 – Prevalence of antimicrobial use in nursing homes in Belgium and the EU/EEA, 2016-2017 ECDC PPS

	Number of NHs	Number of eligible residents	Number of residents with at least 1 antimicrobial*	Observed prevalence (%; 95% CI)	Mean prevalence of NHs (%)	Median prevalence of NHs (IQR)
Belgium (Sciensano report)¹⁴⁴	158 [£]	16 215	900	NR	5.5	5.0 (Min: 0.0-Max: 18.3)
Belgium (international publication)¹⁴³	79	8 206	482	5.9 (5.4-6.4)	5.8	5.1 (2.9-8.1)
EU/EEA	1 788	102 301	5 035	4.9 (4.8-5.1)	5.8	3.6 (0-8.5)

Antimicrobial:* Antimicrobial agents for systemic use within ATC groups A07AA (intestinal anti-infectives), D01BA (dermatological antifungals for systemic use), J01 (antibacterials for systemic use), J02 (antimycotics for systemic use), J04 (antimycobacterials) when used for treatment of mycobacteria (including tuberculosis) or as reserve for multidrug-resistant bacteria and P01AB (nitroimidazole-derived antiprotozoals) were included. Antiviral agents were not included; £: including 130 NH in Flanders, 24 in the Walloon region and 4 in Brussels; NR: not reported; EU/EEA: 24 European Union/European Economic Area countries.

Source: Ben Abdelhafidh and Latour, 2017¹⁴⁴; Ricchizzi et al., 2018¹⁴³

NHs: Nursing Homes; CI: Confidence Interval; IQR: Interquartile range



ANTIBIOTICS PRESCRIBED IN NURSING HOMES

Antibacterials for systemic use (J01) accounted for 94.6% and 95.4% of all antimicrobial prescriptions in Belgium (based on 158 nursing homes) and in the EU/EEA, respectively.^{143, 144} Within the group of antibacterials, the most frequently reported subgroups in Belgian nursing homes were: other antibacterials (J01X: 40.6%), penicillins (J01C: 26.9%) and quinolones (J01M: 15.5%) (Table 10).¹⁴⁴ At the EU/EEA level, the top three antibacterials were the same, but in a different ranking: penicillins (J01C: 30.2%), other antibacterials (J01X: 18.6%) and quinolones (J01M: 14.9%).^{143, 144}

Table 10 – Use of antibiotics (ATC group J01) in nursing homes in 2016-2017

ATC group J01	Proportion of total use	
	Belgium (878 AB prescriptions from 158 NH)	EU/EEA (5 098 AB prescriptions from 1 788 NH)
Tetracyclines (J01A)	1.8%	NR
Penicillins (J01C)	26.9%	30.2%
Other beta-lactam antibacterials (J01D)	2.3%	12.6%
Sulfonamides and trimethoprim (J01E)	2.4%	13.3%
Macrolides, lincosamides and streptogramins (J01F)	10.4%	NR
Quinolone antibacterials (J01M)	15.5%	14.9%
Other J01 substances (J01X)	40.6%	18.6%
Sum (J01B, J01G, and J01R)	0.2%	NR
Other groups	-	10.4%

AB: Antibiotic; NH: Nursing Home

Source: Ben Abdelhafidh and Latour, 2017¹⁴⁴; Ricchizzi et al., 2018¹⁴³

INDICATIONS FOR ANTIMICROBIAL USE

The majority of antimicrobials recorded in the 158 Belgian nursing homes were prescribed for therapeutic reasons (63.8%), another 35.8% for prophylaxis and the indication was missing for the remaining 0.4%.¹⁴⁴ At the EU/EEA level the respective proportions were 69.5%, 29.4% and 1.1%.¹⁴³ Overall, the urinary tract was the most common site for which antimicrobials were prescribed (50.4% in Belgium and 46.1% in EU/EEA), followed by the respiratory tract (31.5% and 29.4%, respectively) and skin or wound (8.8% and 12.6%, respectively).^{143, 144}

In Belgian nursing homes, no less than 78.9% of the total of 332 antimicrobial agents that were prescribed prophylactically, were prescribed to prevent a urinary tract infection (UTI). Hence, 28.2% of all prescribed antimicrobial molecules served as uroprophylaxis. The most frequently used antimicrobial agents for prophylaxis of UTI were nitrofurantoin (J01XE01, 34.0%, n = 85), phosphomycin (J01XX01, 34.0%, n = 85) and nifurtinol (J01XE02, 32.0%, n = 80).¹⁴⁴ In the EU/EEA, the most frequently used antimicrobials for that indication were trimethoprim (J01EA01: 29.7%), nitrofurantoin (J01XE01: 27.0%), methenamine (J01XX05: 11.6%), cephalexin (J01DB01: 6.1%) and fosfomycin (J01XX01: 5.9%).¹⁴³

4.3.1.4 Self-medication with antibiotics

In the 2016 Eurobarometer survey (see Box 20), 95% of Belgian respondents reported that they obtained their last course of antibiotics from their healthcare provider; hence, a slight increase in comparison with the 2013 survey (92%)(Table 11).⁵³ At the EU level, the respective proportion was 93% in 2016. By far the most common source of antibiotics was a medical prescription in Belgium (84%) as well as in the 28 EU member states (73%), but another 11% (and 20% for the EU-28) received antibiotics directly from a medical practitioner (Table 11). There is a persistent minority who still uses antibiotics without a prescription (4% in Belgium and 5% in EU-28) or use those left over from a previous course (1% in Belgium and 2% in EU-28).⁵³

**Box 20 – Eurobarometer survey**

Since 2009, the Directorate-General for Health and Consumers (European Commission) has monitored the levels of public use of and knowledge about antibiotics through three EU wide surveys in 2009, in 2013 and in 2016.⁵³ During the last survey, carried out in April 2016, some 27 969 respondents aged 15 years and over from different social and demographic groups residing in the 28 Member States of the European Union were interviewed face-to-face at home in their mother tongue; in Belgium 1 007 people were interviewed by TNS Dimarso.⁵³ For more information the reader is referred to https://ec.europa.eu/health/amr/sites/amr/files/eb445_amr_generalreport_en.pdf.

Table 11 – Ways of obtaining antibiotics in Belgium and the 28 EU member states in 2016

	Belgium (%)	EU-28 (%)
From a medical prescription	84	73
Administered by a medical practitioner	11	20
You had some left over from a previous course	1	2
Without prescription from a pharmacy	3	4
Without prescription from elsewhere	1	1
Don't remember	0	0
Don't know	0	0
Total 'From a medical practitioner'	95	93
Total 'Not from a medical practitioner'	5	7

Note: Answer to the question 'How did you obtain the last course of antibiotics that you used?' – only one answer possible (answers are formulated as posed in the survey). EU-28: average of the 28 EU member states

Source: Special Eurobarometer Report 445, 2016⁵³

At the EU-28 level, important differences between socio-demographic groups were reported (data not reported at the Belgian level):⁵³

- Women (95%) were slightly more likely than men (90%) to have obtained their last course of antibiotics from a medical practitioner;
- Older respondents (≥ 55 years old: 96%) were more likely than younger people (15-24 years old: 87%) to have obtained antibiotics from a medical practitioner;
- Respondents who answered at last three out of four questions assessing knowledge about antibiotics correctly (cf. infra; 96%) were slightly more likely to have obtained their last course of antibiotics from a medical practitioner than those respondents who answered not more than two questions correctly (89-91%).

4.3.1.5 Reasons for taking antibiotics

According to the 2016 Eurobarometer survey (see Box 20), bronchitis (21%), rhinopharyngitis (13%), skin or wound infections (12%) and the flu (11%) were the most frequently cited reasons for taking antibiotics in Belgium; the respective proportions for the EU-28 were 18%, 7%, 6% and 16% (see Table 12).⁵³ Notably, the most common answer was non-specific, with over a fifth (21% in Belgium and 23% in EU-28) of respondents saying that they took antibiotics for reasons other than the list of options given to them.⁵³

**Table 12 – Reasons for taking antibiotics in Belgium and the 28 EU member states in 2016**

	Belgium (%)	EU-28 (%)
Pneumonia (an infection causing an inflammation of one or both lungs)	5	6
Bronchitis (inflammation and swelling of the bronchi, the airways that carry airflow from the trachea into the lungs)	21	18
Rhinopharyngitis (inflammation of the mucous membrane of the nose and pharynx)	13	7
Flu	11	16
Cold	7	11
Sore throat	7	14
Cough	5	9
Fever	6	11
Headache	4	5
Diarrhea	2	1
Urinary tract infection	7	10
Skin or wound infection	12	6
Other	21	23
Don't know	0	1
<i>Illness only</i>	43	34
<i>Symptom only</i>	29	28
<i>Illness and symptom</i>	7	14

Note: Answer to the question 'What was the reason for last taking the antibiotics that you used?' – multiple answers possible (answers are formulated as posed in the survey). EU-28: average of the 28 EU member states.

Source: Special Eurobarometer Report 445, 2016⁵³

4.3.1.6 Knowledge on antibiotics

According to the 2016 Eurobarometer survey (see Box 20), half of the Belgian population (54%) was aware that antibiotics are ineffective against viruses, which is higher than the EU-28 average (43%; Table 13).⁵³ Nearly three fourths of Belgian respondents (73%) gave the correct answer that antibiotics are not effective against cold and flu, a proportion that was higher than the EU-28 average (56%). A large majority of Belgians and Europeans (both 84%) were aware that overuse of antibiotics reduces their effectiveness, yet, only 60% and 66% of Belgian and European respondents, respectively knew that frequent use of antibiotics can cause side-effects. In Belgium, 29% of respondents answered all four questions correctly, which was slightly higher than the EU-28 average (24%).⁵³

**Table 13 – Overall knowledge about antibiotics in Belgium and the 28 EU member states in 2016**

Is it true or false?	Belgium			EU-28		
	Correct	Incorrect	Don't know	Correct	Incorrect	Don't know
Antibiotics kill viruses	54	39	7	43	46	11
Antibiotics are effective against colds and flu	73	23	4	56	36	8
Unnecessary use of antibiotics makes them become ineffective	84	12	4	84	8	8
Taking antibiotics often has side-effects such as diarrhoea	60	23	17	66	14	20

Source: *Special Eurobarometer Report 445, 2016*⁵³

When asked whether in the last 12 months, the respondent received any information about not taking antibiotics unnecessarily, for example for a cold or the flu, 48% of the Belgian interviewees responded affirmative, which was higher than the EU-28 average (33%).⁵³ Among the Belgian respondents the most quoted sources of this information (multiple answers possible) were a TV advertisement (43%), a professional or health care facility (39%) a conversation with a medical doctor (34%) and the radio (24%); the respective proportions at EU-28 level were 27%, 40%, 32% and 11%.⁵³

Key messages

- In 2017, the total use of antibiotics for systemic use in the Belgian ambulatory sector was 21.1 DID, which is higher than the EU/EEA population-weighted mean of 18.4 DID.
- In the same year, the total use of antibiotics for systemic use in the Belgian hospital sector was 1.64 DID, just below the EU/EEA population-weighted mean of 1.8.
- On the day of the ECDC point prevalence survey (PPS) 28.1% of the hospitalised patients received at least one antimicrobial.
- The reason for antimicrobial use was documented in the patient's medical record for 80.8% of all antimicrobials

prescribed in Belgian hospitals, which is comparable to EU/EEA results (i.e. 80.2%).

- About half of all antimicrobials used in Belgian hospitals, were prescribed for a community-acquired infection (51.4% in Belgium and 49.5% in EU/EEA). The proportion of antimicrobials prescribed for an acute hospital-acquired infection was higher in Belgium than in the EU/EEA (24.2% and 19.6%, respectively).
- The duration of surgical prophylaxis in Belgian hospitals was in 43.8% one dose, in 32.4% one day and in 23.9% more than 1 day, which is better than at the EU/EEA level where 54.2% of surgical prophylaxis courses were prescribed for more than 1 day.
- For hospital-acquired infections, combinations of penicillins, incl. beta-lactamase inhibitors and fluoroquinolones are more often prescribed in Belgium than in the EU/EEA (25.1% vs. 19.8% and 13.0% vs. 9.4%), while the use of carbapenems in these situations is lower (6.7% vs. 9.9%). First-generation cephalosporins are given as surgical prophylaxis to 70.5% of the patients in Belgium; the EU/EEA average is only 26.6%.
- On the day of the ECDC PPS, 5.9% of Belgian nursing home residents received at least one antimicrobial agent, which was higher than the EU/EEA crude, pooled prevalence of 4.9%. The urinary tract was the most common site for which antimicrobials



were prescribed (50.4% in Belgium and 46.1% in EU/EEA), followed by the respiratory tract (31.5% and 29.4%, respectively) and skin or wound (8.8% and 12.6%, respectively).

- In the 2016 Eurobarometer survey, 95% of Belgian respondents reported that they obtained their last course of antibiotics from their healthcare provider. In the same survey, half of the Belgian respondents (54%) was aware that antibiotics are ineffective against viruses, which is higher than the EU-28 average (43%).

4.3.2 Veterinary sector

4.3.2.1 Antimicrobial use in Belgian food-producing and companion animals

The 2018 BelVet-Sac report, presenting data for 2017, shows a continued positive evolution with a reduction of 7.4% mg active substance/kg biomass in comparison to 2016; this corresponds in absolute numbers with a decrease in the use of antimicrobial compounds of -8.3% subdivided in a decrease of -1.6% in pharmaceuticals and -46.3% in antibacterial premixes (Figure 12).¹³¹ This is the highest reduction in antibiotic use in the Belgian veterinary sector in one year ever observed.

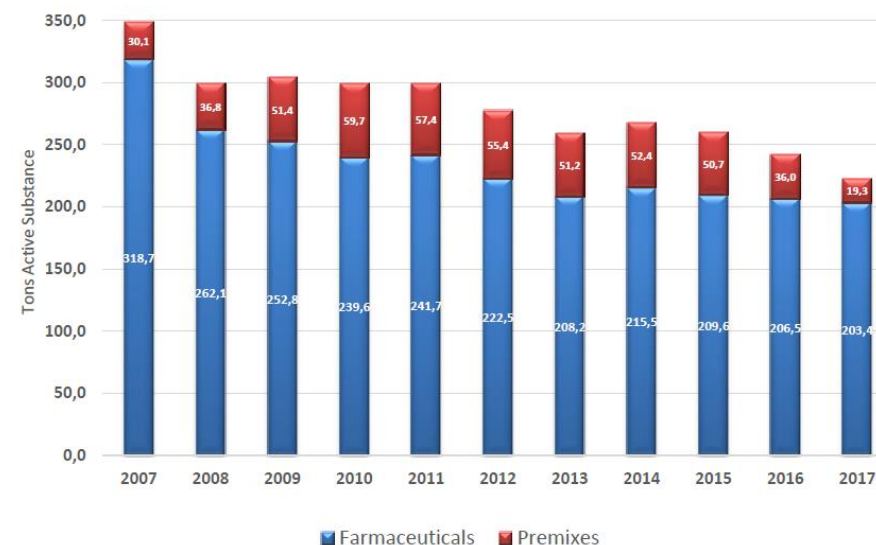
Split up in pharmaceuticals and premixes, there was since 2011 a decline of 16.4% and 66.6%, respectively. For the latter 2017 was the second year with a substantial reduction. For this indicator the 2020 AMCRA objective (i.e. a reduction of 50%) has already been achieved (see Box 12 in section 3.4.3).^{128, 131}

Compared to 2011⁹⁹, a total reduction of 25.9% (mg active substance/kg biomass) in antibiotic use has been achieved. The decrease is observed for the majority of antibiotic classes, however the reduction was most pronounced for the quinolones (-64.2%) and the 3rd and 4th generation cephalosporins (-65.9%). The decrease of sulphonamides (-31.8%) and

polymyxins (-13.3%) was also significant.^{128, 131} In comparison to 2011, the cumulative reduction of 'red' molecules (i.e. 3rd and 4th generation cephalosporins and fluoroquinolones, see also section 6.2.2.2) was 84.4%. In other words, the second AMCRA goal (i.e. a reduction of 75% by 2020) has also been achieved.

Overall, the objective of a 50% reduction in total antibiotic use by 2020 is not yet within reach. The coming years an annual reduction of 8% is needed to reach AMCRA's 2020 goal.^{128, 131}

Figure 12 – Total national use of antibacterial compounds for veterinary use in Belgium for the years 2007-2017, expressed as tons active substance



Source: BelVet-Sac report 2017¹³¹

⁹⁹ For the AMCRA 2020 goals, which were adopted by the Belgian government in 2016, the year 2011 is the reference year (see also section 3.4.3 - Box 12).



Monitoring of the evolution in antibiotic use per animal species remains partial^{hh} with the BelVet-Sac data, because many products are registered for multiple species. Nevertheless from the 2017 report it appears that the main reductions in use are accomplished in pig and poultry production. This observation is not surprising because of the substantial decline in antibiotics in medicated feed, which is almost exclusively used in pig farming.^{128, 131}

4.3.2.2 *Antimicrobial use in Belgian food-producing and companion animals, in a European context*

The eighth ESVAC report reveals that the Belgian sales of veterinary antimicrobial agents equalled in 2016 140.1 mg sold per population correction unit^b (PCU); among the 30 participating European countries the sales ranged between 2.9 mg/PCU and 453.4 mg/PCU, the weighted mean was 124.6 mg/PCU and the median was 57.0 mg/PCU (Table 14).¹⁴¹

In Belgium, the largest amounts of antibiotics, expressed as a proportion of mg/PCU, were accounted for by penicillins (35.8%), tetracyclines (20.7%) and sulfonamides (22.6%); the respective proportions at European level were 25.8%, 32.3% and 11.6%. Taken together, these three classes accounted for 79.1% and 69.7% of the total sales for food-producing animals in Belgium and Europe, respectively, in 2016.

From the antimicrobial classes listed in the WHO list of the highest priority critically important antimicrobials (CIAs) for human medicine (see Box 21), the sales for food-producing animals of 3rd and 4th generation cephalosporins, fluoroquinolones, polymyxins and macrolides accounted for 0.2%, 0.4%, 1.7% and 7.2%, respectively, of the total sales in Belgium.¹⁴¹

^{hh} BelVet-Sac data do not allow reporting at animal species level. However, species are clustered together in larger groups, for example poultry. In addition, 99% of all premix in feed antibiotics are intended for pigs. This way groups of species (e.g. poultry, pigs) can be identified.



Table 14 – Sales of the various antimicrobial classes for food-producing animals in 2016

Antimicrobial class ^{\$}	Mg/PCU					
	Belgium		Total for 30 European countries		Median [#] of 30 European countries	
Tetracyclines	29.0	20.7%	40.3	32.3%	21.2	37.2%
Amphenicols	1.8	1.3%	1.6	1.3%	0.7	1.2%
Penicillins	50.1	35.8%	32.1	25.8%	12.9	22.6%
1 st and 2 nd generation Cephalosporins	0.2	0.1%	0.1	0.1%	0.1	0.2%
3 rd and 4 th generation Cephalosporins	0.3	0.2%	0.2	0.2%	0.2	0.4%
Sulfonamides	31.7	22.6%	14.4	11.6%	7.2	12.6%
Trimethoprim	6.4	4.6%	2.4	1.9%	1.1	1.9%
Macrolides	8.7	6.2%	8.7	7.0%	3.7	6.5%
Lincosamides	2.7	1.9%	3.8	3.0%	0.4	0.7%
Fluoroquinolones	0.6	0.4%	2.7	2.2%	1.0	1.8%
Other quinolones	0.4	0.3%	0.5	0.4%	0.0	0.1%
Aminoglycosides	0.5	0.4%	6.4	5.1%	2.5	4.4%
Polymyxins	2.4	1.7%	6.4	5.1%	1.0	1.8%
Pleuromutilins	0.6	0.4%	3.5	2.8%	1.3	2.3%
Others*	4.9	3.5%	1.5	1.2%	0.6	1.1%
Total mg/PCU	140.1		124.6		57.0	

^{\$}: In the ESVAC reports sales are reported by classes/subclasses independent of whether or not this refers to a single or a combination product — i.e. not by ATCvet classes; *: Other antibacterials include bacitracin, fosfomycin, furaltadone, metronidazole, novobiocin, paromomycin, rifaximin and spectinomycin; #: median shows the average of 15th and 16th values ranked from smallest to largest per each variable of 30 observations.

Source: 8th ESVAC report 141



Box 21 – WHO list of critically important antimicrobials

Because the use of antimicrobials in food-producing animals is an important source of antimicrobial resistant bacteria that humans can be exposed through food supply, the WHO has developed and applied criteria to rank antimicrobials according to their relative importance in human medicine.¹⁴⁷ The rationale behind it is that an improved management of the use of antimicrobials in food animals, particularly reducing those critically important for human medicine, is an important step towards preserving the benefits of antimicrobials for people. Clinicians, regulatory agencies, policy-makers and other stakeholders can use this ranking when developing risk management strategies for the use of antimicrobials in food-producing animals.¹⁴⁷

The antimicrobials are grouped into three categories based on their importance to human medicine: important, highly important and critically important antibiotics, subdivided in high priority and the highest priority.

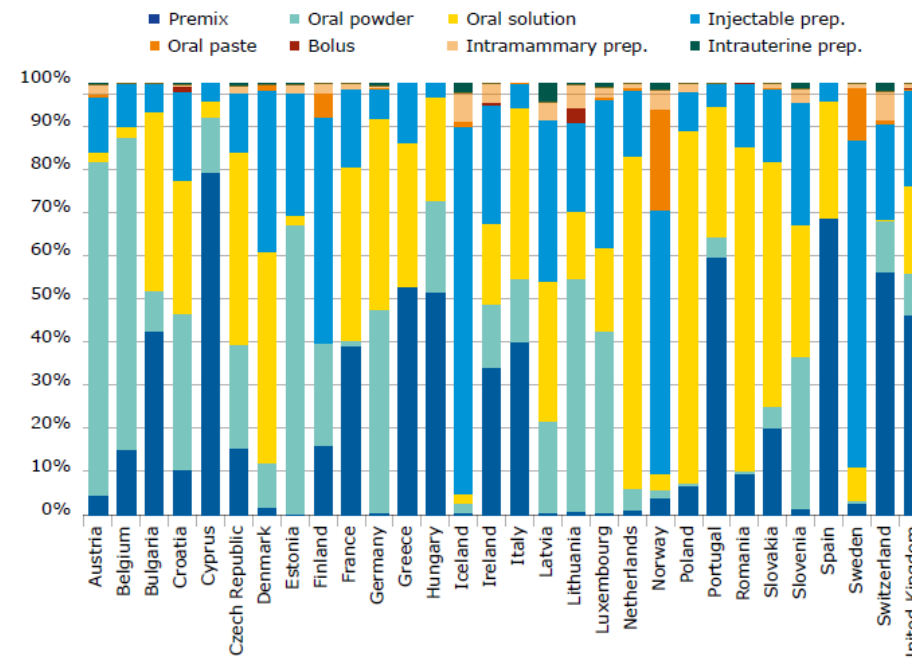
Critically important antimicrobials (CIA's) with highest priority are (3rd, 4th, 5th generation) cephalosporins, glycopeptides, macrolides and ketolides, polymyxins, quinolones. These antibiotics are essential as last-resort treatments for multidrug-resistant infections in humans.

CIA's with high priority are aminoglycosides, ansamycins, carbapenems and other penems, glycyclines, lipopeptides, monobactams, oxazolidinones, penicillins, phosphonic acid derivatives, and drugs used solely to treat tuberculosis or other mycobacterial diseases.¹⁴⁷

The World Organisation for Animal Health (OIE) also developed a list of CIA's which converges to some extent (e.g. 3rd and 4th generation cephalosporins, macrolides and fluoroquinolones) with the WHO list.¹⁴⁸

Aggregated across the 30 countries, the sales (mg/PCU) of pharmaceutical forms for group treatment accounted for the vast majority of the total sales (90.1%): premixes accounted for 40.8%, oral powders for 11.9% and oral solutions for 37.4%.¹⁴¹ As can be deduced from Figure 13, the distribution of sales of veterinary antimicrobial agents for food-producing animals varied considerably between countries; no exact data were provided per country.

Figure 13 – Distribution of sales of veterinary antimicrobial agents for food-producing animals, in mg of active substance per population correction unit^b (mg/PCU), by pharmaceutical form in 30 European countries for 2016



Tablets are not included in the data as these are used almost solely in companion animals.

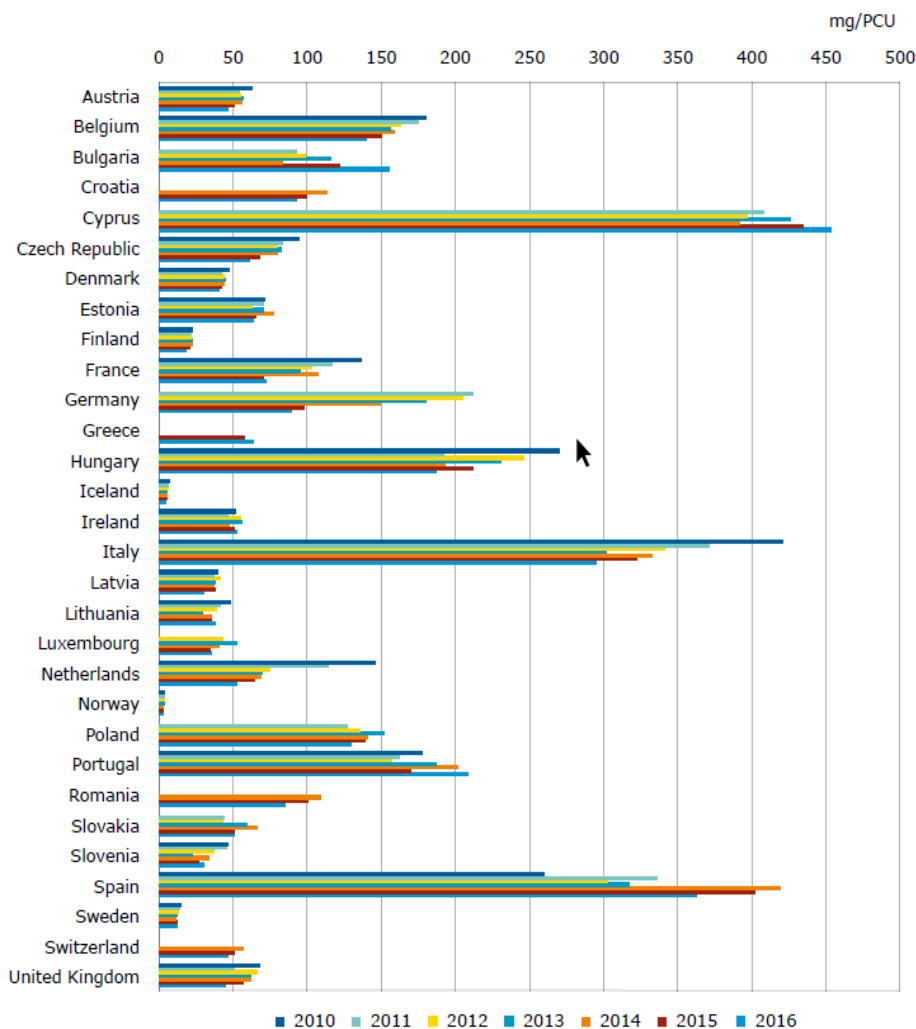
Source: 8th ESVAC report ¹⁴¹

Trends in antibiotic use over time

Between 2010 and 2016, the use of veterinary antimicrobial agents in Belgium decreased by 22% from 180 mg/PCU to 140 mg/PCU (Figure 14). A drop in antimicrobial use was also observed for 15 other European countries (ranging from 8.7 % to 57.8 %). On the other hand, an increase (ranging between 7.9% and 67.7%) was noted in Bulgaria, Cyprus, Greece, Portugal and Spain.¹⁴¹



Figure 14 – Total sales of veterinary antimicrobial agents for food-producing species, in mg/PCU, from 2010 to 2016, for 30 European countries



Note: Bulgaria: data are under-reported for 2011, 2012 and 2014 as several wholesalers failed to report data; the Czech Republic: strength reported as the base for most veterinary medicinal products (VMPs) for 2011-2012 for; for 2013-2016, strength reported as in the label of the VMPs; the Netherlands: strength reported as the base for some VMPs for 2011-2012; for 2013-2016, strength reported as in the VMPs' label; Romania: 2014 data were updated, as wholesalers initially failed to deliver all sales data; Slovakia: for 2011 and 2012, the data represent antimicrobial VMPs imported by wholesalers; from 2013 data represent all sales from wholesalers to end-users (veterinarians, pharmacies, producers of medicated feeding stuffs and farmers, obtained by import and from national manufacturers); Spain: under-reporting for the years 2010 to 2013 has been identified (underestimated); UK: high sales of certain tetracycline-containing products late in 2010 were probably used in 2011 and thus their use has been underestimated for 2011.

Source: 8th ESVAC report ¹⁴¹

Figure 15 provides an overview of the overall antibiotic sales for food-producing animals in mg/PCU in 2016, with the highest users of antibiotics in the South of Europe and the lowest in the North.



Figure 15 – Spatial distribution of overall sales of all antimicrobials for food-producing animals, in mg/PCU, for 30 countries, for 2016



Source: 8th ESVAC report ¹⁴¹



Key messages

- Compared to 2011, a total reduction of 25.9% (mg active substance/kg biomass) in antibiotic use in the Belgian veterinary sector has been achieved. The coming years an annual reduction of 8% is needed to reach AMCRA's 2020 goal.
- The decrease is observed for the majority of antibiotic classes, however the reduction was most pronounced for the quinolones (-64.2%) and the 3rd and 4th generation cephalosporins (-65.9%). The decrease of sulphonamides (-31.8%) and polymyxins (-13.3%) was also significant.
- Split up in pharmaceuticals and premixes, there was since 2011 a decline of 16.4% and 66.6%, respectively. Hence, for the latter the 2020 AMCRA objective (i.e. a reduction of 50%) has already been achieved.
- The ESVAC report reveals that the Belgian sales of veterinary antimicrobial agents equalled in 2016 140.1 mg/PCU, hence higher than the European mean (124.6 mg/PCU) and more than double the European median (57.0 mg/PCU).

4.4 Antibiotic use in the Belgian ambulatory and hospital sector further explored

4.4.1 Methods

This section presents the results of a further exploration of data on antibiotic use in the Belgian ambulatory and hospital sector, based on reimbursement data for the period 2014-2016 provided by RIZIV – INAMI. The analyses are restricted to ATC group J01, i.e. antibacterials for systemic use. The DDDs were calculated by RIZIV – INAMI according to the 2019 WHO table (see section 4.3.1).

The definitions of broad and narrow spectrum antibiotics for the ambulatory and hospital sector, are based on the respective definitions provided in the joint ECDC, EFSA and EMA report (2017).¹⁴⁹ For the ambulatory sector the ratio broad to narrow spectrum antibiotics was calculated as follows: broad-spectrum penicillins, cephalosporins, macrolides and fluoroquinolones (J01(CR+DC+DD+(F-FA01)+MA)) to narrow-spectrum penicillins, cephalosporins and macrolides (J01(CA+CE+CF+DB+FA01)). For the hospital sector, the proportion of broad-spectrum antibiotics (i.e. piperacillin in combination with a beta-lactamase inhibitor (J01CR05), third- and fourth-generation cephalosporins (J01DD and J01DE), monobactams (J01DF), carbapenems (J01DH), fluoroquinolones (J01MA), glycopeptides (J01XA), polymyxins (J01XB), daptomycin (J01XX09) and oxazolidinones, linezolid (J01XX08) and tedizolid (J01XX11)) on the total DDD was calculated.

The number of inhabitants was estimated through the number of people covered by the compulsory insurance (i.e. 10 910 061 or 98.0% of the Belgian population on 1 January 2014, 10 954 480 or 97.9% of the Belgian population in 2015 and 10 997 963 or 97.8% of the Belgian population in 2016). Antibiotic treatment was defined according to the IMA – AIM definition i.e. 'one or more package(s) of antibiotics with the same national code number (CNK)ⁱⁱ, prescribed by the same prescriber and reimbursed to a

ⁱⁱ The CNK is an ordering number with no analytical signification. It is attributed to all medicine and parapharmaceutical products on the basis of their name, galenic form, composition, dosage, packaging and marketing authorization.¹⁵⁰



beneficiary within a period of 7 days'. For the number of practitioners the definition of RIZIV – INAMI was used: the number of health professionals with at least one reimbursed procedure performed on 31 December 31 of the given year.^{jj} The number of patient days was provided by RIZIV – INAMI.

Information on prescribers' qualifications was available only for the ambulatory sector. They were grouped in ten subgroups, i.e. general practitioner (GP), paediatrician, ear-nose and throat, pneumologist, dermatologist, gynaecologist-obstetrician, specialist in internal medicine, other specialists, dentist and midwife. Doctors without clinical specialisation were classified in the GP group. Physicians who hold several specialisations were classified according to the first specialisation cited in the RIZIV – INAMI code, whereas physicians 'in training' were grouped in the corresponding graduated physicians' group.

The data comprise antibiotic use in acute care as well as chronic care hospitals. However, the databases did not include antibiotic use in the psychiatric hospitals because several stratification variables (e.g. age, ATC code, type of unit) were not available. Hospital departments were first grouped in inpatient versus day care. Inpatient wards were further subdivided in seven groups, i.e. paediatric ward, geriatric and revalidation ward, intensive care unit, burn unit, diagnostic and medical treatment ward, diagnostic and surgical treatment ward and other inpatient wards^{kk}.

About 10% of the Belgian nursing homes buy their medication through hospital pharmacies. The data for these nursing homes were not included in the ambulatory nor in the hospital database.

In order to have an estimate of the exposure rate to antibiotics, the proportion of citizens with at least one antibiotic delivery (i.e. with at least one ATC J01 code) was calculated by RIZIV – INAMI based on Belgian InterMutualist Agency (IMA – AIM) data. This indicator was extracted from KCE report 313 (<https://kce.fgov.be/en/performance-of-the-belgian-health-system-%E2%80%93-report-2019>). The ratio amoxicillin (ATC code J01CA04) to amoxicillin-clavulanate^s (J01CR02) was also calculated for the ambulatory sector because one BAPCOC objective for the period 2014-19 is to change this ratio from 50/50 to 80/20 by 2018.⁷⁷ A reduction of the quinolone use by 50% was also an objective of the BAPCOC plan and was therefore also evaluated.

The analyses were performed using the R software version 5.3.1.¹⁵¹

^{jj} For more info, see 'Number of health practitioners with a proven practice by profession and specialty'. Available at: <https://www.inami.fgov.be/fr/statistiques/soinsdesante/2016/Pages/nombre-dispenseurs-soins-individuels.aspx> (last access: 14 January 2019).

^{kk} Other inpatient wards: non-intensive neonatal care, infectious disease ward, maternity ward, re-education ward, child and adult neuropsychiatry and

psychiatry ward and specialized ward for treatment and functional rehabilitation of patients with a defined health state (e.g. cardiopulmonary diseases, locomotor diseases, neurological conditions, chronic conditions requiring palliative care, chronic conditions requiring prolonged medical care and psychogeriatric conditions)



4.4.2 Results

4.4.2.1 Use of antibiotics in the ambulatory sector

TOTAL ANTIBIOTIC USE

In 2016, the number of DDD per 1000 inhabitants per day (DID) was **22.9** in the ambulatory sector which corresponds to a slight decrease of 1.7% (or an average annual decrease of 0.2 DID) in respect to the year 2014 (Table 15)^{II}. These results are in line with the data presented by ECDC in the ESAC-Net interactive website and discussed in section 4.3.1.1. The slight difference may be explained by the fact that the ESAC-Net estimates are calculated on the total number of inhabitants while we used the total number of insured individuals as denominator.

In 2016, the **number of treatments per 1000 inhabitants per day (TID)** was **2.3**. Based on these two indicators (DID and TID), we can state that the use of antibiotics in the Belgian ambulatory sector stayed **stable over the period 2014-16** (Table 15).

The proportion of inhabitants with **at least one antibiotic delivered** was **39.6%** in 2016 (Table 15), which means that more than 39.6% of the Belgian population was exposed to at least one antibiotic in 2016. This corresponds to a decrease of 2% compared to the year 2013.

Table 15 – Indicators for any antibiotic use (ATC group J01) in the ambulatory sector, by year

Indicator	2013	2014	2015	2016	Average annual change 2014-2016
Number of DDD per 1000 inhabitants per day	NA	23.3	23.9	22.9	-0.20
Number of treatments per 1000 inhabitants per day	NA	2.3	2.3	2.3	0.02
Proportion of inhabitants with at least one antibiotic delivered (%)	41.7*	NA	NA	39.6**	NA

*Results from KCE report on the performance of the Belgian health system 2015;¹⁵² **Results from KCE report 313 (<https://kce.fgov.be/en/performance-of-the-belgian-health-system-%E2%80%93-report-2019>); DDD: defined daily dose; NA= Not available.

^{II} The results presented in Table 15 are lower than those presented in the IMA – AIM atlas for the same period of time (i.e. 26.7 DIDs, 27.6 DIDs and 29.2 DIDs for 2016, 2015 and 2014 respectively) (Atlas IMA-AIM, available at: <https://aim-ima.be/Atlas> (last access: 8 January 2019)). These differences may be explained by the fact that IMA – AIM does not apply the same acceptability filters on data as RIZIV – INAMI. When RIZIV-INAMI receives data on antibiotic use from the sickness funds, it ensures the quality, completeness and reliability of data through more than 50 defined rules. If the data received do not satisfy the established quality rules, they are sent back to the sickness fund which is asked to correct them. Finally, in the RIZIV-

INAMI data the DDDs were calculated according to the 2019 WHO table, which had the impact of reducing the overall number of DDDs for the years 2014 to 2016. The 2019 update includes modifications in DDDs for eight antibacterials (ampicillin from 2g to 6g, oral amoxicillin from 1g to 1.5g, parenteral amoxicillin from 1g to 3g, oral amoxicillin with beta-lactamase inhibitor from 1g to 1.5g, cefepime from 2g to 4.5g, meropenem from 2g to 3g, parenteral ciprofloxacin from 0.5g to 0.8g and parenteral colistin from 3g to 9g). Available at:

https://www.whooc.no/news/new_atc_ddd_included_in_the_index_of_2019 (last access: 25 January 2019).



ANTIBIOTIC USE BY PATIENT CHARACTERISTICS

Women (43.8%), inhabitants older than 65 years (44.6%), and among the elderly (≥ 75 years) those in nursing homes (62.2%) and citizens from Hainaut (45.2%) were most frequently exposed to at least one antibiotic in 2016 (Table 16).

Table 16 – Proportion of inhabitants with at least one antibiotic delivered, by patient characteristics, 2016

Variable	Category	Proportion with ≥ 1 antibiotic
Age (years)	0 to 14 years	38.2%
	15 to 64 years	38.6%
	65+ years	44.6%
Gender	Female	43.8%
	Male	35.4%
Place of residence (75 years old or more)	In nursing home	62.2%
	Not in a nursing home	44.4%
Province	Antwerpen	36.0%
	Brabant Wallon	39.1%
	Brussels capital	35.3%
	Hainaut	45.2%
	Liège	43.8%
	Limburg	42.7%
	Luxembourg	42.4%
	Namur	43.9%
	Oost-Vlaanderen	37.5%
	Vlaams Brabant	38.4%
	West-Vlaanderen	40.9%

Source: IMA – AIM; calculation: INAMI – RIZIV; Results from KCE report 313 (<https://kce.fgov.be/en/performance-of-the-belgian-health-system-%E2%80%93-report-2019>).

The group of inhabitants aged **65 years and older** used more antibiotics than the inhabitants aged 15-64 years, expressed in DID or in TID (Table 17). A similar amount of antibiotics is used by children 0-14 years of age and the 15-64 age group, expressed in TID (DID being not a suitable metric for children, as said above).

Table 17 – Antibiotic use in the ambulatory sector in DID and TID, by age-group of the patient, 2016

Age-group of the patient (in years)	Number of DDD per 1000 inhabitants per day	Number of AB treatment per 1000 inhabitants per day
0-14	10.2*	2.0
15-64	22.7	2.0
65+	34.3	3.3

DDD: defined daily dose; * may be underestimated (see Box 13)

There is some geographical variation in antibiotic use in Belgium (Figure 16). Based on the province of the prescriber, Namur had in 2016 the highest antibiotic use when expressed in DID and Brussels capital region and Antwerp had the lowest DID (Table 18). However, these differences should be interpreted with caution, since they may also be correlated with the socio-demographic structure of the population (e.g. age, sex, level of income, proportion of elderly in nursing homes) and therefore do not only reflect a difference of antibiotic prescription practices



Table 18 – Use of any antibiotic (ATC group J01) in the ambulatory sector, by province of the prescriber, 2016

Province of the prescriber	Number of DDD per 1000 inhabitants per day	Ranking
Antwerp	19.8	10
Walloon Brabant	25.9	2
Brussels capital	19.4	11
Hainaut	23.4	8
Liège	25.1	3
Limburg	24.4	5
Luxembourg	23.8	7
Namur	27.5	1
East Flanders	22.1	9
Vlaams Brabant	24.7	4
West Flanders	24.1	6
Median [P25;P75]	24.1 [22.1;25.1]	

DDD: defined daily dose; P25: first quartile; P75: third quartile

ANTIBIOTIC USE BY PRESCRIBER CHARACTERISTICS

General practitioners contributed most to antibiotic use in the ambulatory sector in Belgium (76.6% of total DDD). Paediatricians ranked fifth in the proportion of the total DDD (1.9% of total antibiotic DDD) in 2016, but fourth in the proportion of total treatments (3.4% of total antibiotic treatments) (Table 19). This difference in ranking is not surprising, given the fact that antibiotic use in children is underestimated when expressed in DDD (see Box 13). When taking into account the number of practitioners per medical specialty, we also observed that general practitioners (5 570 DDDs per health practitioner), dermatologists (4 383 DDDs per health practitioner) and pneumologists (2 078 DDDs per health practitioner) were the most important antibiotic prescribers in the ambulatory sector in 2016 (Table 19).

General practitioners prescribed mainly amoxicillin (ATC code J01CA04, 23.4% of the total DDD prescribed), amoxicillin-clavulanate^s (ATC code J01CR02, 21.2% of the total DDD prescribed) and azithromycin (ATC code J01FA10, 8.4% of the total DDD prescribed), while dermatologists used mainly amoxicillin (66.3% of the total DDD prescribed) and minocycline (ATC code J01AA08, 21.1% of the total DDD prescribed). Pneumologists prescribed mainly azithromycin (ATC code J01FA10, 44.9% of the total DDD prescribed), amoxicillin-clavulanate (ATC code J01CR02, 17.7% of the total DDD prescribed) and moxifloxacin (ATC code J01MA14, 9.4% of the total DDD prescribed).

Figure 16 – Number of DDD per 1000 inhabitants per day (DID), by province of the prescriber, 2016

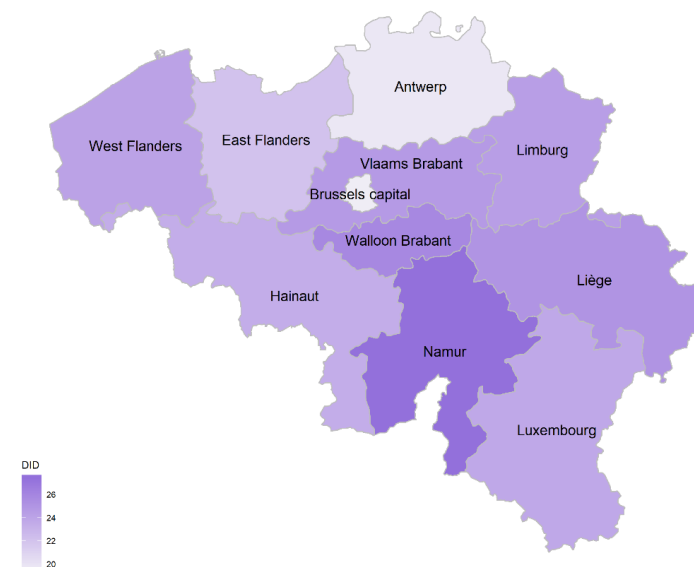




Table 19 – Antibiotic use in the ambulatory sector, by type of prescriber, 2016

Type of prescriber	Proportion of total DDD	Ranking (total DDD)	Proportion of total treatment	Ranking (total treatment)	Number of DDD per health practitioner*	Ranking (DDD by 100 practitioners)
General practitioner	76.6%	1	75.7%	1	5 570	1
Paediatrician	1.9%	5	3.4%	4	1 205	6
Ear-nose and throat	1.2%	7	1.2%	8	1 704	4
Pneumologist	1.2%	7	0.81%	9	2 078	3
Dermatologist	3.5%	4	1.7%	5	4 383	2
Gynaecologist-obstetrician	1.1%	9	1.3%	7	719	7
Specialist in internal medicine	1.6%	6	1.5%	6	1 565	5
Other specialist	7.7%	2	7.4%	2	NA	NA
Dentist	5.1%	3	7.0%	3	569	8
Midwife	<0.1%	10	<0.1%	10	25	9

*: The denominator is the number of health practitioner with a least one proven practice on December 31, 2015 (both ambulatory and hospital sector), used as proxy of the total number of prescribers in the ambulatory sector (the definition of a health practitioner is given in section 4.4.1); DDD: defined daily dose; NA: not available.

Male prescribers contributed most to antibiotic use in the ambulatory sector (**63.4% of total DDD**). Yet, it has to be realised that despite a feminisation of the medical profession in the last years in Belgium, male prescribers are still more numerous in Belgium.¹⁵³ Due to data constraints we could not calculate the number of DDD by prescriber and by gender.

The group of prescribers aged **56 to 65 years** contributed most to the antibiotic use in the ambulatory sector (**34.4% of total DDD**), while the group of prescribers aged 20-35 years contributed the least (16.5% of the total DDD) (Table 20). However, these age groups represent cohorts of different sizes. Again, due to data constraints we could not calculate the number of DDD by prescriber and by age group. In addition, it is important to mention that some age misclassification may occur as some practitioners in training may prescribe (some) antibiotics on the prescription notes of their supervisor.

Table 20 – Antibiotic use in the ambulatory sector, by age group of the prescriber, 2016

Age-group of the prescriber (in years)	Proportion of total DDD
20*-35	16.5%
36-45	17.1%
46-55	22.7%
56-65	34.4%
65+	9.4%

*The lower bound of this age-group is unknown, 20 years was arbitrarily chosen as lowest possible age to prescribe an antibiotic; DDD: defined daily dose

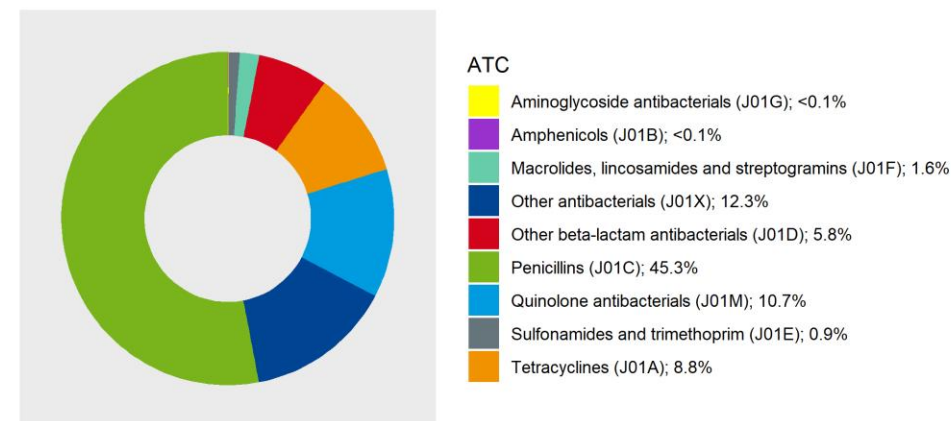


ANTIBIOTIC USE BY ATC CODE

Penicillin (ATC code J01C) was the **most used** antibiotic in 2016 in the ambulatory sector (Figure 17).

In 2016 the highest proportion of penicillin out of the total antibiotic use expressed in DDD, was observed in the age group 0-14 years (Table 21). Most commonly used penicillins in children (0-14 years) were amoxicillin (75% of total penicillin DDD in 0-14 years) and the association amoxicillin and a beta-lactamase inhibitor such as clavulanates (23.6% of total penicillin DDD in 0-14 years) (Table 22). It should be noted that DDD is a metric based on an adult dosage and DDD in children are thus more difficult to interpret (see Box 13).

Figure 17 – Proportion of the total DDD in the ambulatory sector, by ATC code, 2016



Proportion of total DDD

DDD: defined daily dose

Table 21 – Antibiotic use in the ambulatory sector per ATC code, in proportion of total antibiotic use in DDD, by age-group, 2016

ATC code	0-14 years Proportion of total DDD	15-64 years Proportion of total DDD	65 + Proportion of total DDD
Tetracyclines (J01A)	4.5%	11.2%	4.9%
Amphenicols (J01B)	0.1%	0.1%	0.1%
Penicillins (J01C)	70.4%	46.5%	35.8%
Other beta-lactam antibacterials (J01D)	4.2%	5.9%	6.2%
Sulfonamides and trimethoprim (J01E)	0.4%	0.8%	1.4%
Macrolides, lincosamides and streptogramins (J01F)	17.5%	16.6%	14.7%
Aminoglycoside antibacterials (J01G)	0.2%	0.1%	0.0%
Quinolone antibacterials (J01M)	0.6%	9.9%	15.2%
Other antibacterials (J01X)	2.0%	9.2%	21.8%

DDD: defined daily dose

Table 22 – Penicillins (J01C) use in 0 to 14 years per ATC code, in proportion of total penicillin use in DDD, 2016

ATC code (J01C)	Proportion penicillins of total DDD
Ampicillin (J01CA01)	<0.1%
Amoxicillin (J01CA04)	74.5%
Phenoxymethylpenicillin (J01CE02)	0.2%
Flucloxacillin (J01CF05)	1.7%
Amoxicillin and beta-lactamase inhibitor (J01CR02)	23.6%

DDD: defined daily dose

Other antibacterials (ATC code J01X) represented 12.3% of the total DDD use (Figure 17), and in the age group ≥ 65 years even 21.8% (Table 21). ATC code J01X includes more particularly nitrofurantoin, which is mainly used to treat urinary tract infections (Table 23).

Table 23 – Use of other antibacterials (J01X) in the ≥ 65 age group, 2016

Other antibacterials (J01X)	Proportion of total DDD
Nitrofurantoin (J01XE01)	49.0%
Nifurtoinol (J01XE02)	44.6%
Fosfomycin (J01XX01)	6.4%
Spectinomycin (J01XX04)	<0.1%
Others*	<0.1%

* Vancomycin (J01XA01), Teicoplanin (J01XA02), Colistin (J01XB01). DDD: defined daily dose

An objective in the BAPCOC's 2014-19 plan (see Box 10) was to decrease the quinolone use in the ambulatory sector from 10% of the total antibiotic use in 2014 to 5% by 2018.⁷⁷ In 2016 the **quinolone** use was still **10.7% of the total DDD** for the ambulatory sector, hence far away from the BAPCOC objective (Figure 17). The highest ratio quinolone to total antibiotic use expressed in DDD was observed in the age group ≥ 65 years (Table 21). Stratification by province of the prescriber indicates that the geographical variation is limited (Table 24).

Table 24 – Proportion quinolone of the total DDD in the ambulatory sector, by province of the prescriber, 2016

Province	Proportion quinolones (ATC code J01M) of total DDD
Antwerp	11.1%
Walloon Brabant	10.2%
Brussels capital	9.5%
Hainaut	10.3%
Liège	9.7%
Limburg	11.3%
Luxembourg	9.2%
Namur	9.8%
East Flanders	11.3%
Vlaams Brabant	11.1%
West Flanders	11.4%

DDD: defined daily dose

ANTIBIOTIC USE: BROAD VS. NARROW SPECTRUM

The majority of antibiotics used in the ambulatory sector in 2016 were **broad spectrum** antibiotics (ratio broad to narrow spectrum: **2.26**). The elderly (≥ 65 years) are the most exposed to broad-spectrum antibiotics (Table 25). The ratio broad to narrow antibiotics did not vary much between Belgian provinces (range 1.94 to 2.93) (Figure 18).

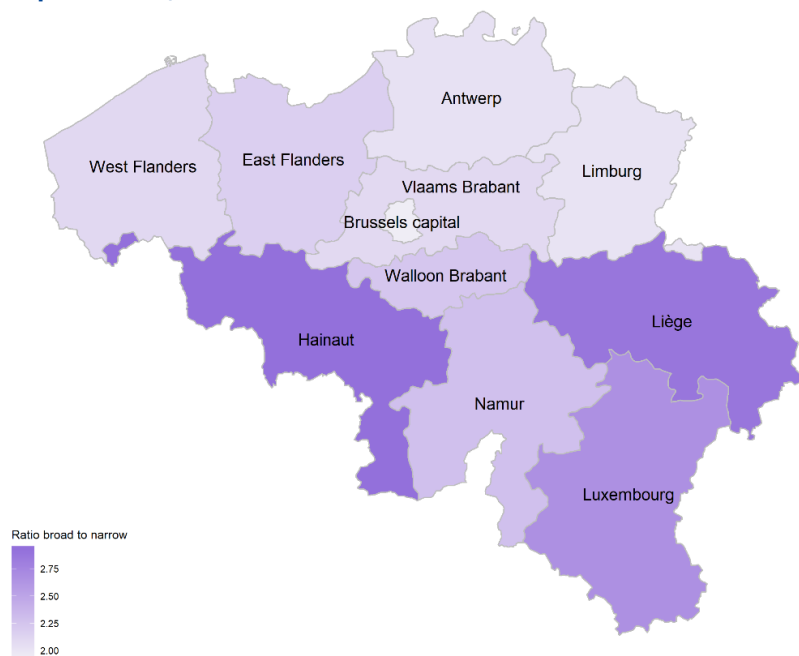


Table 25 – Ratio* broad to narrow spectrum antibiotics in the ambulatory sector, by year and age-group

Age-group	2014	2015	2016
0-14 years	0.74	0.72	0.67
15-64 years	2.44	2.45	2.28
65 + years	4.09	4.04	3.84
Total	2.42	2.43	2.26

*Use of broad-spectrum penicillins, cephalosporins, macrolides and fluoroquinolones (J01(CR+DC+DD+(F-FA01)+MA)) to the use of narrow-spectrum penicillins, cephalosporins and macrolides (J01(CA+CE+CF+DB+FA01))

Figure 18 – Ratio broad to narrow spectrum antibiotics, by province of the prescriber, 2016



ANTIBIOTIC USE: AMOXICILLIN VS. AMOXICILLIN – CLAVULANATE

An objective in the BAPCOC 2014-19 plan (see Box 10) was to reach an amoxicillin to amoxicillin-clavulanate ratio of 80/20 by 2018,⁷⁷ as amoxicillin-clavulanate has a limited role as first-line treatment for ambulatory infections.¹⁵⁴ The analysis of the data indicate a slight improvement of this ratio from 2014 (0.86) to 2016 (1.02), but the ratio in 2016 was still far from the BAPCOC objective (Table 26). For this indicator important **differences** exist between **age groups**: in the 0-14 years old, this ratio has progressively increased to 3.16 in 2016, thus close to BAPCOC's objective (Table 26).

Table 26 – Ratio amoxicillin to amoxicillin-clavulanate in the ambulatory sector, by year and age-group

Age-group	2014	2015	2016
0-14 years	2.65	2.86	3.16
15-64 years	0.84	0.86	0.98
65 + years	0.53	0.55	0.63
Total	0.86	0.88	1.02

ANTIBIOTIC USE: GENERIC VERSUS NOT GENERIC

In 2016, **56.5%** of the total antibiotic use (in DDD) in the ambulatory sector was **generic** (Table 27). Penicillins were the most frequently used in a generic form (69.6% of the DDD for ATC code J01C), followed by quinolones (68.2%) and macrolides, lincosamides and streptogramins (66.1%).



Table 27 – Proportion generic antibiotics out of the total DDD per ATC code, in the ambulatory sector, 2016

ATC code	Proportion generic of total DDD, by ATC
Tetracyclines (J01A)	51.0%
Amphenicols (J01B)	0.0%
Penicillins (J01C)	69.6%
Other beta-lactam antibacterials (J01D)	43.9%
Sulfonamides and trimethoprim (J01E)	0.0%
Macrolides, lincosamides and streptogramins (J01F)	66.1%
Aminoglycoside antibacterials (J01G)	27.3%
Quinolone antibacterials (J01M)	68.2%
Other antibacterials (J01X)	<0.1%
Total	56.5%

DDD: defined daily dose

4.4.2.2 Use of antibiotics in the hospital sector

TOTAL ANTIBIOTIC USE

In 2016, **1.68 DDD per inhabitant per day** was used in the hospital sector (including acute and chronic care), which corresponds to a slight increase (2.1%) compared to 2014 (Table 28). The number of DDD per 1000 hospital stays decreased slightly between 2014 and 2016.^{mm}

Estimates in the hospital sector are slightly different from the results presented in the ESAC-Net website (1.67 DIDs, 1.68 DIDs and 1.71 DIDs in 2014, 2015 and 2016, see section 1.1.1.1). In addition to the possible

^{mm} The data (per patient day and per stay) presented here differ slightly from the data presented in the most recent BeH-SAC report (Sciensano).¹⁵⁵ This can be explained (among others) by the fact that in the present report data for

explanations described above, these differences may also be ascribed to the fact that the RIZIV – INAMI data which were used for this report, did not include psychiatric hospitals.

Table 28 – Antibiotic use in the hospital sector, by year, 2014-16

Indicator	2014	2015	2016	Average annual change 2014-2016
Number of DDD per 1000 inhabitants per day	1.65	1.67	1.68	0.02
Number of DDD per 1000 patient days	NA	199	198	NA
Number of DDD per 1000 stays	1162	1139	1097	-32.43

NA: not available. DDD: defined daily dose

ANTIBIOTIC USE BY PATIENT CHARACTERISTICS

The use of antibiotics in hospitals presents a comparable age distribution as in the ambulatory sector, with the **elderly** using **most** (207 DDDs per 1000 patients days) (Table 29).

acute care and chronic care hospitals are included, while in the BeH-SAC report data are restricted to the acute care hospitals. Moreover, we used the 2019 WHO table to calculate the DDDs, whereas in the BeH-SAC report the 2018 WHO table was used.

**Table 29 – Antibiotic use in the hospital sector, by age-group of the patient, 2016**

Age-group (in years)	Number of DDD per 1000 inhabitants per day	Number of DDD per 1000 patient days
0-14	0.5	164
15-64	1.0	191
65+	5.1	207

DDD: defined daily dose

ANTIBIOTIC USE BY HOSPITAL WARD

In 2016, the highest amounts of antibiotics were used in the diagnostic and medical treatment wards (33.7% of the total DDD), followed by the diagnostic and surgical treatment wards (25.7%) and the geriatric and revalidation wards (15.6%). Nevertheless, by taking into account the number of patient days by ward, which is a better indicator to benchmark the different units, the **intensive care units** (ICU) rank highest, with **536 DDDs per 1000 patient days** in 2016. In other words, for each day of hospitalization in the ICU more than one patient on two received an antibiotic.

Table 30 – Antibiotic use in the hospital sector, by ward, 2016

Service	% total DDD	Number of DDD per 1000 inhabitants per day	Number of DDD per 1000 patients days
Day ward	2.5%	<0.1	36
Paediatric ward	4.3%	0.1	257
Geriatric and revalidation ward	15.6%	0.26	209
Intensive care unit	9.0%	0.2	536
Burn unit	0.1%	<0.1	358
Diagnostic and medical treatment ward	33.7%	0.6	277
Diagnostic and surgical treatment ward	25.7%	0.4	277
Other classical units ¹	9.1%	0.2	82

¹ Non-intensive neonatal care section, contagious diseases service, maternity service, re-education service, child and adult neuropsychiatry and psychiatry service and specialized service for treatment and functional rehabilitation of patients with defined health state (cardiopulmonary diseases, locomotor diseases, neurological conditions, chronic conditions requiring palliative care, chronic conditions requiring prolonged medical care and psychogeriatric conditions). DDD: defined daily dose



This finding corroborates the last Belgian PPS report, where it was observed that 52.7% (95% CI 48.6-56.7) of the patients hospitalised in the intensive care unit used at least one antimicrobial on the day of the PPS (see section 1.1.1.1).¹⁴⁰ **Burn units** (358 DDDs per 1000 patients days) and **medical and surgical wards** (277 DDDs per 1000 patient days in both units) ranked second and third. A high use of antibiotics is also observed in the paediatric ward (257 DDDs per 1000 patients days) given an expected underestimation of the antibiotic use when using the DDD as metric (see section 4.1.1) (Table 30).

ANTIBIOTIC USE BY ATC CODE

As in the ambulatory sector, penicillins (ATC code J01C) were used the most in 2016 in the hospital sector (46.8% of the total DDD) (Table 31); the differences between age groups was small (Table 32). Quinolone use amounted to 11.5% of the total antibiotic DDD in 2016 which is relatively close to the proportion observed in the ambulatory sector (10.7% in 2016). As expected, they were less frequently used in children (0-14 years: 1.8% total DDD) than in older patients (15-64 years: 9.5%; 65+ years: 13.6%) (Table 32), but again, antibiotic use in children expressed in DDD may be underestimated. Other beta-lactam antibacterials (mainly cefazolin and cefuroxime) are also frequently used in the hospital sector (22.5%) (Table 31).

Table 31 – Antibiotic use in the hospital sector, by ATC code, 2016

ATC code	Proportion of total DDD	Number of DDD per 1000 inhabitants per day	Number of DDD per 1000 patient-days
Tetracyclines (J01A)	0.8%	<0.1	1.5
Amphenicols (J01B)	0.7%	<0.1	1.5
Penicillins (J01C)	46.8%	0.8	92.9
Other beta-lactam antibacterials (J01D)	22.5%	0.4	44.7
Sulfonamides and trimethoprim (J01E)	2.3%	<0.1	4.5
Macrolides, lincosamides and streptogramins (J01F)	6.4%	0.1	12.8
Aminoglycoside antibacterials (J01G)	1.5%	<0.1	3.0
Quinolone antibacterials (J01M)	11.5%	0.2	22.9
Other antibacterials (J01X)	7.4%	0.1	14.7

DDD: defined daily dose



Table 32 – Antibiotic use in the hospital sector in proportion of total antibiotic DDD, by ATC code and by age-group of the patient, 2016

ATC code	0-14 years (% total DDD)	15-64 years (% total DDD)	65 + years (% total DDD)
Tetracyclines (J01A)	0.1%	1.0%	0.7%
Amphenicols (J01B)	7.0%	0.5%	0.4%
Penicillins (J01C)	45.1%	46.1%	47.4%
Other beta-lactam antibacterials (J01D)	23.7%	24.7%	21.0%
Sulfonamides and trimethoprim (J01E)	7.0%	2.1%	2.0%
Macrolides, lincosamides and streptogramins (J01F)	9.6%	6.9%	5.9%
Aminoglycoside antibacterials (J01G)	2.0%	1.8%	1.3%
Quinolone antibacterials (J01M)	1.8%	9.5%	13.6%
Other antibacterials (J01X)	3.7%	7.4%	7.7%

DDD: defined daily dose

ANTIBIOTIC USE: BROAD VS. NARROW SPECTRUM

The majority of antibiotics used in the hospital sector in 2016 were **narrow-spectrum (70.1%** of the total DDD). **Intensive care wards** and **burn units** used the highest proportion of broad-spectrum antibiotics (Table 33).

Table 33 – Proportion of broad-spectrum antibiotic use in the hospital sector, by ward, 2016

Ward type	Proportion broad* spectrum of total DDD
Day ward	25.1%
Paediatric ward	19.2%
Geriatric and revalidation ward	32.1%
Intensive care unit	44.5%
Burn unit	39.8%

Ward type	Proportion broad* spectrum of total DDD
Diagnostic and medical treatment ward	35.5%
Diagnostic and surgical treatment ward	22.0%
Other classical units ¹	19.2%
Total	29.9%

*Broad spectrum antibiotics: J01CR05, J01DD, J01DE, J01DF, J01DH, J01MA, J01XA, J01XB, J01XX09, J01XX08 and J01XX11; Non-intensive neonatal care section, contagious diseases service, maternity service, re-education service, child and adult neuropsychiatry and psychiatry service and specialized service for treatment and functional rehabilitation of patients with defined health state (cardiopulmonary diseases, locomotor diseases, neurological conditions, chronic conditions requiring palliative care, chronic conditions requiring prolonged medical care and psychogeriatric conditions). DDD: defined daily dose.



ANTIBIOTIC USE: AMOXICILLIN VS. AMOXICILLIN-CLAVULANATE

Unlike in the ambulatory sector, **amoxicillin-clavulanate** was **almost always** preferred to amoxicillin alone (ratio equals 0.08 in 2016) in the hospital sector, and no change is observed over the 2014-16 period.

Table 34 – Ratio amoxicillin to amoxicillin-clavulanate in the hospital sector, by year

	2014	2015	2016
Ratio	0.07	0.07	0.08

ANTIBIOTIC USE: GENERIC VS. NOT GENERIC

Overall, **44.5%** of the antibiotics used in the hospital sector were **generic** which is lower than in the ambulatory sector (56.5%). Other beta-lactam antibacterials were the most frequently used in a generic form (73.0%), followed by tetracyclines (ATC code J01A) (49.2%) (Table 35).

Table 35 – Antibiotic use in the hospital sector, proportion generic by ATC code, 2016

ATC code	% DDD Generic, by ATC
Tetracyclines (J01A)	49.2%
Amphenicols (J01B)	0.0%
Penicillins (J01C)	39.8%
Other beta-lactam antibacterials (J01D)	73.0%
Sulfonamides and trimethoprim (J01E)	0.0%
Macrolides, lincosamides and streptogramins (J01F)	32.8%
Aminoglycoside antibacterials (J01G)	43.1%
Quinolone antibacterials (J01M)	32.4%
Other antibacterials (J01X)	34.5%
TOTAL	44.5%

DDD: defined daily dose

Key messages

In the ambulatory sector in 2016:

- The total use of antibacterials for systemic use (ATC group J01) was 22.9 DDD per 1000 inhabitants per day (DID), which corresponds to a slight decrease of 1.7% compared to the year 2014.
- The total number of antibiotic treatments per 1000 inhabitants per day (TID) was 2.3, an increase of 1.8% compared to 2014.
- About 39.6% of inhabitants was delivered at least one antibiotic by a pharmacy open to the public.
- Women (43.8%), inhabitants older than 65 years (44.6%), among the elderly (≥ 75 years) those residing in nursing homes (62.2%) and citizens from Hainaut (45.2%) were most frequently exposed to at least one antibiotic.
- Penicillin (ATC code J01C) was used most.
- The majority of antibiotics were broad-spectrum antibiotics (ratio broad vs. narrow: 2.26).
- The ratio amoxicillin to amoxicillin-clavulanate improved slightly from 0.86 in 2014 to 1.02 in 2016.
- General practitioners (5 570 DDDs per health practitioner), dermatologists (4 383 DDDs per health practitioner) and pneumologists (2 078 DDDs per health practitioner) were the most important antibiotic prescribers.

In the hospital sector in 2016:

- The total use of antibacterials was 1.68 DDD per inhabitant per day in the Belgian hospitals; this is a slight increase (2.1%) compared to 2014.
- Patients admitted in hospital, were prescribed 198 DDDs per 1000 patient days or 1097 DDDs per 1000 hospital stays.



- As in the ambulatory sector, the elderly used most antibiotics (207 DDDs per 1000 patients days).
- Antibiotic use was highest in the intensive care units (536 DDDs per 1000 patient days), the burn units (358 DDDs per 1000 patients days) and the medical and surgical wards (277 DDDs per 1000 patient days in both units).
- Penicillins (46.8% of the total DDD), other beta-lactam antibacterials (22.5%, mainly cefazolin and cefuroxime) and quinolones were the most frequently used antibiotics.
- The majority of antibiotics used in the hospital sector in 2016 were narrow-spectrum (70.1% of the total DDD).
- Amoxicillin-clavulanate was almost always preferred to amoxicillin alone.

5 DETERMINANTS OF ANTIBIOTIC PRESCRIPTION AND USE

5.1 Determinants of antibiotic prescribing in human medicine

This chapter summarises the determinants that influence the prescription of antibiotics for human use, based on a pragmatic literature review. Briefly, we included all primary studies that involved Belgian subjects and were published between January 2000 and April 2018, comprising Belgian reports and other grey literature. We also included systematic reviews published between January 2012 and April 2018 and considered the included primary studies if they were conducted in countries with similar settings (Western Europe and North America). Further details about the methods can be found under Appendix 1.1.

The determinants of the choice of the antibiotic molecule have not been included, nor specific clinical factors triggering antibiotic prescription (e.g. auscultatory findings for acute cough). The interventions influencing antibiotic prescription are described in chapter 6.

Determinants belong to various categories: factors related to the prescriber (e.g. socio-demographic factors, attitudes and beliefs), to the patient (e.g. knowledge and behaviour), to the health care system (e.g. reimbursement system) and to the overall environmental and cultural scheme.

Quantitative and qualitative studies are reported. For quantitative studies, we only included results when the analysis was adjusted for confounding factors and adjusted odd or risk ratios were reported. Most quantitative studies use the rate of antibiotic prescription as a proxy for prudent use. A number of qualitative studies are based on fictitious cases in order to simulate prescribing, using questionnaires, focus groups or face-to-face interviews with GPs.¹⁵⁶

Most studies assessed determinants at individual level (i.e. at the patient and/or prescriber level) but a number of them assessed the correlation between national characteristics (e.g. cultural dimension) and national prescription behaviour. Models of cultural dimensions have been developed by different authors to better understand and measure cultural differences



using various tools.¹⁵⁷⁻¹⁵⁹ The most commonly used tool is the Hofstede cultural dimensions, that have been scored for each country and entered into a database that can be used for correlation analysis with antibiotic use.¹⁶⁰

In this Chapter, we first describe the determinants that influence the prescription of antibiotics, in Belgium (see section 5.1.1) and in similar settings (see section 5.1.2). Determinants are classified according to whether they concern the prescriber, the patient, the culture or the health care system of the country. Next we report other determinants that influence the use of antibiotics by patients (besides the prescription) i.e. self-medication and compliance to treatment (see section 5.1.3).

5.1.1 Determinants of antibiotic prescription in Belgium

This section describes the results of studies involving Belgian prescribers and/or patients, including European studies as well if these involve prescribers from Belgium.

A total of 20 peer-reviewed studies or reports from grey literature published since January 2000 were found: 5 qualitative studies and 15 quantitative analyses, which include 7 database analyses (including prescriptions, prevalence surveys and Eurobarometer). A short description of the study design is provided in Table 53 (see Appendix 1.1). Studies involving prescriber data (n=13) included mostly GP, by interviewing them or analysing their prescription data. One study involved only hospital data (surgical prophylaxis). In five studies patients, members of sickness funds or the general population were interviewed.

Results are presented in Table 36 and the main findings are summarized in the text below.

Table 36 – Determinants of antibiotic prescription in Belgian studies

Determinant	Determinant associated with higher antibiotic use	Sources
<i>Determinants related to the prescriber</i>		
Age / years of practice	Age >40 years (RR=0.7 to 0.8 in <40 years vs. >60 years) ¹⁶¹ Younger GP (35 years vs. 55 years) ¹⁶²	Willaert et al., 2018 ¹⁶¹ , Coenen et al., 2006 ¹⁶²
Gender	Male GP tend to prescribe more but the association is very low	Willaert et al., 2018 ¹⁶¹
Place of residence/practice	Wallonia (RR=1.15 vs. Flanders), ¹⁶¹ Brussels (RR=29 vs. Antwerp) ¹⁶²	Willaert et al., 2018 ¹⁶¹ , Coenen ¹⁶²
Financing scheme for consultations	GP using fee for service vs. lump sum e.g. in some group practices ('maisons médicales' - 'wijkgezondheidscentra')	Feron et al., 2007, ¹⁶³ Tulkens et al., 2016, ¹⁶⁴ INAMI/RIZIV 2015 ¹⁶⁵
Professional training	Trained GP (not intern) vs. GP in professional training GP vs. specialist	Coenen et al., 2006, ¹⁶² Willaert et al., 2008 ¹⁶¹
Uncertainty and fear related to outcome	Outcome uncertainty with fear of complication or severe outcome, having missed severe disease once	Coenen et al., 2006, ¹⁶⁶ Feron et al., 2007 and 2009, ^{163, 167} Tulkens et al., 2016 ¹⁶⁴
Past prescription behaviour	The tendency to prescribe antibiotics in the past (best independent predictor)	De Sutter et al., 2001 ¹⁶⁸
Diagnosis uncertainty	Difficulty to make a diagnosis, lack of rapid diagnostic tools, availability of X-ray	Coenen et al., 2000, ¹⁶⁶ Feron et al., 2007 and 2009, ^{163, 167} Tulkens et al., 2016 ¹⁶⁴



Determinant	Determinant associated with higher antibiotic use	Sources
Chagrin factor or 'better safe than sorry'	GP prefer to prescribe when not necessary than not prescribing when necessary	Coenen et al., 2000, ¹⁶⁶ Tulkens et al., 2016, ¹⁶⁴ Deschepper et al., 2002 ¹⁶⁹
Perceived patient demand for antibiotics	Perceived patient demand on antibiotic prescribing (OR=12 in Coenen et al., 2013) ¹⁷⁰	Coenen et al., 2006, ¹⁶² Feron et al., 2007 and 2009, ^{163, 167, 171} Tulkens et al., 2016, ¹⁶⁴ Coenen et al., 2013 ¹⁷⁰
Disease labelling by GP	E.g. Diagnosis of sinusitis for running nose	De Sutter et al., 2001 ¹⁶⁸
Time per patient and timing of consultation	Time pressure, insufficient time to spend with the patient, timing of consultation before a WE or before holidays	Feron et al., 2007 and 2009, ^{163, 167} Tulkens et al., 2016 ¹⁶⁴
Confidence in guidelines	Lack of confidence in guidelines, considered to be motivated by financial aspects, and feeling of coercion from authorities.	Feron et al., 2007 and 2009, ^{163, 167, 171}
GP-patient relationship	Needs of efficacy, feel obligation of fast result, fear to loose patient	Feron et al., 2007 and 2009, ^{163, 167, 171} Tulkens et al., 2016 ¹⁶⁴
NOT AB resistance	The risk of bacterial resistance was not playing a role in daily practice	Feron et al., 2007 and 2009 ^{163, 167}
<i>Determinants related to the patient</i>		
Age, gender	Age <3 years and >85 years Women > men	Willaert et al., 2018, ¹⁶¹ Feron et al., 2009 ¹⁷¹
Place / residence	West Flanders, Wallonia (RR=1.3 vs. Flanders), large towns, districts bordering France	Willaert et al., 2018, ¹⁶¹ Van Eldere et al., 2007, ¹⁷² INAMI/RIZIV 2015 ¹⁶⁵
Education	Lower educational level (primary school)	Meeus et al., 2018 ¹⁷³
Patient knowledge	Lack of knowledge on AB effects (lack of effectiveness on virus infection, side effects and risk of resistance)	Borg, 2012 ¹⁵⁸
Patient anxiety	High patient or parent anxiety	Feron et al., 2007 and 2009 ^{163, 171}
Disease severity and patient vulnerability perceived by physician	Disease severity and fragility of the patient (comorbidities, frailty, living in a nursing home) as perceived by GP, socio-economic factors	Willaert et al., 2018, ¹⁶¹ Coenen et al., 2006, ^{162, 174} Feron et al., 2007 and 2009, ^{163, 171} Tulkens et al., 2016 ¹⁶⁴
Clinical picture	Clinical picture with low specificity (e.g. bronchitis, coloured sputum)	Coenen et al., 2000, ¹⁶⁶ Feron et al., 2007 and 2009, ^{163, 171} Tulkens et al., 2016. ¹⁶⁴
Disease perception and labelling by patient	Disease perceived as serious, more visits to the doctor, disease labelled as bronchitis, importance of pain relief, coping with self-limiting infections, health care seeking behaviour	Deschepper et al., 2002, ¹⁶⁹ van Driel et al., 2006, ¹⁷⁵ Van Duijn et al., 2003 ¹⁷⁶
Attitudes and expectations for AB	Patient expecting (OR 2.1) or hoping for (OR=2.5) antibiotics Not patient asking for antibiotics (OR=0.6)	Coenen et al., 2013, ¹⁷⁰ van Driel et al., 2006 ¹⁷⁵ Coenen et al., 2006 ¹⁶²
Needing a medical note	Patient needing a medical note for a sick or school leave	Van Driel et al., 2006 ¹⁷⁵



Determinant	Determinant associated with higher antibiotic use	Sources
<i>Determinants related to the health care system</i>		
Consultation rates	High consultation rates (national level)	Tyrstrup et al., 2017 ³⁵
Reimbursement for AB	AB being cheap drugs	Feron et al., 2007, ¹⁶³ Tulkens et al., 2016 ¹⁶⁴
Fee-for-service	Health system with predominance of fee-for-service	Coenen et al., 2000, ¹⁶⁶ Feron et al., 2007 ¹⁶³
<i>Determinants related to country characteristics</i>		
Religious background	Catholic background (vs. protestant in the NL)	Deschepper et al., 2002 ¹⁶⁹
Distance to power**	High distance to power, i.e. patients feel little need for involvement	Deschepper et al., 2008 ¹⁷⁷
Uncertainty avoidance**#	High uncertainty avoidance, i.e. physicians feel the urge to 'do something' and patients want a clear cause / label of disease	Deschepper et al., 2008, ¹⁷⁷ Borg, 2012, ¹⁵⁸ Borg, 2014 ^{159#}
Masculinity vs. femininity**	High 'masculinity' culture, i.e. result oriented and 'live to work' ethics	Borg, 2012 ¹⁵⁸
Influenza season	Higher influenza season	Willaert et al., 2018 ¹⁶¹

GP: General practitioner; AB: antibiotic(s); RR: relative risk or risk ratio; OR: odd ratio; NL: the Netherlands. **: According to Hofstede's cultural dimensions. Large distance to power in medicine refers to contexts where patients treat doctors as superiors, and consultations are shorter and controlled by the doctor ('doctor knows best' attitude). Uncertainty avoidance refers to tolerance of a society for uncertainty and ambiguity. In medicine, patients and physicians are expected to avoid any risk, prefer clear labelling of diseases and to start presumptive treatment. Masculinity refers to the distribution of roles between genders: masculine dimensions are very assertive and competitive. #: in that study, Belgium was an outlier in the association between uncertainty avoidance and surgical prophylaxis, due to a (short term) financial intervention (see section 6.1.2)

5.1.1.1 Place

The prescription of antibiotics is associated with the geographical place of the GP practice or the residence of the patient in all quantitative studies including geographical variable(s) in the analysis. The places with higher antibiotic prescription rates were districts from West Flanders,¹⁶¹ areas close to the French border (Namur, Luxembourg),^{161, 165, 172} or Wallonia in general.¹⁶¹

5.1.1.2 Factors related to the prescriber

Determinants related to characteristics of the prescriber include age and/or years of practice, being a GP (compared to specialist), using the fee for service system (vs. lump sum), having high consultation rates and feeling time pressure.^{161, 163, 164, 167} Age and years of practice are obviously related, and physicians prescribing more antibiotics tended to be older in a national study of the Socialist Sickness Fund (SSF): GPs below 40 years of age

prescribed 20-30% less antibiotics in 2008-16 than GPs ages 60 years or more.¹⁶¹ However in a study among Flemish GPs, GPs around 35 years of age prescribed more antibiotics for acute cough in adults than GPs around 55 years of age, as prescription by younger GPs was more associated with perceived patient demand (see below).¹⁶² The influence of age was considered to be rather due to a cohort effect: a study comparing the prescription of specific antibiotics showed that physicians partly maintain antibiotic prescribing habits of the past as they age.¹⁷⁸

Studies including a comparison of fee for service vs. lump sum showed a higher risk of antibiotic prescription in case of fee for service, but the association was not always significant.^{162, 165} A qualitative study among GPs highlighted that in the fee for service system, GPs feel a need to justify the "service paid" by a prescription, and to avoid to ask patients to come back if there is no improvement.¹⁶³ In addition, GPs in professional training tended to prescribe less.¹⁶²



A Ghentⁿⁿ study showed that GPs have very divergent prescribing behaviour of antibiotics for common cold or sinusitis, from no antibiotics for any encounter to antibiotics at every encounter.¹⁶⁸ The personal habit of the individual GP to prescribe antibiotics for acute upper respiratory infections (individual antibiotic prescribing rate) was the best predictor of whether a patient will be prescribed antibiotics, before any patient characteristics. A study in Flemish GPs did not find differences in antibiotic prescription and quality indicators for consultations during office hours versus out-of-hours.¹⁷⁹

The qualitative studies mostly explored why and when GPs tended to prescribe antibiotics. A number of qualitative studies involved GPs from one side of the country only (either Wallonia alone, or Flanders alone), and it is unclear whether results can be extrapolated to the entire country. However three motives were identified in most studies from both communities:

- The GP perception that patients want or demand antibiotics: this was the most frequently identified motive and there was a poor agreement with whether the patient actually wanted antibiotics or not.^{162-164, 167, 170, 171}
- Uncertainty and fear regarding the patient diagnosis and the evolution of the disease episode: this other frequent motive may relate to the fact that Belgium is a country with a high score of uncertainty avoidance (see below).^{163, 164, 166, 167, 169, 171}
- The 'chagrin factor', a term used in qualitative decision analysis, or 'better safe than sorry': this relates to the preference to prescribe when not necessary rather than not prescribing when necessary,^{164, 166, 169} and is probably related to the latter determinant, including the absence of a clear etiological diagnosis in most ambulatory cases.

In three studies among French speaking GPs, two additional motives were identified: the lack of confidence in existing guidelines and the GP-patient relationship.^{162, 163, 171, 180} Guidelines developed by health authorities were seen by GPs as financially motivated. Besides, Belgian guidelines do not take into account the lack of an etiological diagnosis that prevails in usual GP practice: guidelines present how to prescribe antibiotics for specific

diagnoses, which are supposed to be accurate.¹⁶³ GPs also tend to prescribe more antibiotics when they feel obliged to provide fast results and reach efficacy.^{163, 164, 167, 171} Antibiotic resistance was not a motive for a more prudent antibiotic use in the studies including that factor.^{167, 171}

5.1.1.3 Patient factors

Patients to which more antibiotics were prescribed had the following factors:

- Age: young children and elderly;^{161, 171}
- Considered by the physician to present a higher disease severity and to be more fragile;^{161-164, 167, 171, 174}
- Lower educational and socio-economic level, including living conditions and patient ability to come for a second consultation;^{163, 173}
- Patient or parent anxiety;^{163, 167, 171}
- Knowledge of antibiotic effect, including the lack of effectiveness against viruses, side effects and the detrimental long-term effect on resistance;¹⁵⁸
- Demanding, expecting or hoping for antibiotic treatment;^{170, 175}
- Consulting their GP more often and calling their disease bronchitis;^{169, 175}
- Needing a medical note for a sick or school leave.¹⁷⁵

A study of patients in three EU countries including Belgium revealed that Belgian patients report a greater perceived need to consult a GP when presenting respiratory tract infection (RTI) and considered these symptoms more serious than those from the UK and the Netherlands.¹⁷⁶ A higher proportion of patients believed that antibiotics speed up recovery in case of RTI. A Belgian study looking at patients who want antibiotics for sore throat (regardless of physician prescriptions) revealed that the desire for pain relief

ⁿⁿ Located in Flanders.



and thinking that antibiotics speed up recovery from sore throat were the major motives to ask for an antibiotic.¹⁶⁸

We did not find any study on the determinants of antibiotic prescription or use in Belgian nursing homes, or long-term care facilities in general. Although the prevalence of patients receiving an antibiotic in these facilities is high and regularly measured by the HALT surveys (see section 4.2.1.2), these surveys do not describe the determinants of antibiotic use.^{121, 181, 182}

5.1.1.4 Factors of the health care system

Factors of the Belgian health care system that favour antibiotic prescription are the fee for service system that is more frequent in Belgium than the lump sum system (see above), high consultation rates (when comparing to other countries), and the fact that co-payments for antibiotics are usually low (for the patient).^{35, 163, 164} A qualitative study reported that the organization of health care in Belgium, where there is no official relationship between doctors and patients and where most doctors are paid by fee for service, may also explain some of the excessive use of antibiotics.¹⁶⁶ It also referred to an older study comparing GP attitudes in Belgium, Britain and the Netherlands, which showed that GPs in Belgium had the highest level of 'disease-centred' attitudes (vs. patient-centred), which in previous studies was correlated with increased prescribing of symptomatic medication.^{183, 184} Another study of antibiotic use in the same three countries hypothesizes that being more directly dependent on patients for income (i.e. fee for service) may be a risk factor for higher antibiotic use prescribed by GPs.¹⁸⁵ It also pointed to the high number of GPs in Belgium: in 2005, Belgium had four times more GPs per 1000 persons (1.9) than the Netherlands (0.48) and antibiotic prescription was 2.4 times higher (24 vs. 10 DDD per 1000 persons per day).¹⁸⁵

5.1.1.5 Cultural factors

Cultural characteristics of the country were also found to influence antibiotic prescription in international studies that included Belgium, and are presented as possible explanations of the high prescription rate in Belgium compared to some other EU countries.^{159, 169, 177, 186}

A qualitative study compared the attitude of 30 citizens affected by upper respiratory tract infection (URTI) in two towns at 60 km distance, one in Belgium (Bruges) and one in the Netherlands (Middelburg).¹⁶⁹ The study associated the higher use of antibiotics in Belgian subjects (31% vs. 9% in Dutch participants) to the catholic background vs. protestant in the Netherlands. Catholic Flemish participants had a different attitude towards disease compared to Dutch participants: they had less trust in the self-healing power, feared complications when no medicines were used, felt uncertain, and uncertainty was an element to contact a doctor more easily. They labelled more commonly their URTI 'bronchitis' and reported that they frequently used antibiotics for bronchitis. The study concluded that the reflex 'illness = seeing a doctor = medicines' led to a higher use of antibiotics; it also warned that **simply copying the more restrictive Dutch organisation of health care in order to improve antibiotic use in Belgium will not be sufficient due to cultural differences.**¹⁶⁹

Three cultural dimensions described by Hofstede were found to be associated with high prescription and use of antibiotics in three studies that included Belgian subjects:^{158, 159, 177}

- Low distance to power, i.e. patients feel little need for involvement in medical decisions and believe that 'doctor knows best';¹⁷⁷
- High uncertainty avoidance, i.e. tolerance of a society for uncertainty and ambiguity. Physicians feel the urge to 'do something' and patients are likely to have difficulties with accepting to manage their viral respiratory infection with simple rest and symptomatic treatment;^{158, 159, 177}
- Masculinity i.e. the distribution of roles between genders in the society.¹⁵⁸ Countries with a high masculinity score are very assertive, driven by competition, achievement and success and have a strong



work ethos. Antibiotics may be seen as vital tools to get back to work as quickly as possible.

Belgium scores high among the 27 EU countries studied regarding uncertainty avoidance (3rd) and power distance (9th), according to the 2010 Hofstede scores, and is in the middle range for masculinity (13th).¹⁵⁸ The high masculinity score of Belgium also seems to corroborate a 2018 qualitative study among members of the socialist sickness fund, who report that they feel obliged to come back to work as soon as possible.¹⁷³ The difference between Flanders and Wallonia is mostly in masculinity, on which Wallonia scores higher (60) than Flanders (43) according to Hofstede scores.⁰⁰

The two dimensions uncertainty avoidance and masculinity explained nearly half of the variation of inappropriate use of antibiotics for cold, flu and sore throat reported in the Eurobarometer survey according to a quantitative study of all EU countries.¹⁵⁸ It should be noted, as comparison, that the Netherlands has one of the lowest EU score for uncertainty avoidance (21th on 26) and masculinity (24th on 26).¹⁵⁸

5.1.1.6 Other determinants

In the qualitative study of the SSF, 73% of (Dutch speaking) respondents considered that physicians should more clearly oppose to patients who are asking for an antibiotic.¹⁶¹

None of the 20 studies conducted among Belgian prescribers identified the influence of the pharmaceutical industry marketing (e.g. visits from advisors) on antibiotic prescription. Although this role is difficult to assess in quantitative studies, it was not identified in qualitative studies using focus groups and in-depth interviews either.

5.1.2 Determinants of antibiotic prescription in other regions

In total, five systematic reviews assessing the determinants of antibiotic prescription and published in 2012-2018 have been retrieved:^{156, 157, 187-189}

- Touboul-Lundgren et al., 2015. Identification of cultural determinants of antibiotic use cited in primary care in Europe.¹⁵⁷
- Md Reza et al., 2015. Physicians' knowledge, perceptions and behaviour towards antibiotic prescribing: a systematic review of the literature.¹⁸⁸
- Public Health England (PHE) 2015. Behaviour change and antibiotic prescribing in health care settings.¹⁸⁹
- Teixeira Rodrigues et al., 2013. Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies.¹⁸⁷
- Lopez-Vazquez et al., 2012. Misprescription of antibiotics in primary care: a critical systematic review of its determinants.¹⁵⁶

The main characteristics of these reviews are summarized in Table 54 (see Appendix 1.1). They covered primary studies published between 1987 and 2015, but the inclusion criteria differed across reviews. Three included both quantitative and qualitative studies,^{157, 188, 189} one review included only quantitative studies,¹⁵⁶ and the last review included only qualitative studies.¹⁸⁷ Three reviews covered inpatient as well as outpatient levels of care,¹⁸⁷⁻¹⁸⁹ and two of them were limited to ambulatory care.^{156, 157} One review was restricted to cultural determinants assessed in multi-country studies, and included three studies on self-medication (described under section 5.1.3).¹⁵⁷ The more recent review, i.e. covering studies up to 2015, only covered the country-level cultural determinants in ambulatory care in Europe.¹⁵⁷ The Public Health England (PHE) review was limited to the behaviours that drive resistance and did not describe quantitative results.¹⁸⁹

⁰⁰ <https://www.hofstede-insights.com/country/belgium/>



In addition, 26 primary studies have been retrieved, some of them to further explore the associations described in the reviews (when this was deficient),^{177, 190-203} and others because they were not included in the reviews (e.g. more recent or topics not covered).²⁰⁴⁻²¹⁵

Overall, the systematic reviews and other studies confirmed the findings of the Belgian studies, but some additional determinants were also identified, as summarized in Table 37, Table 39 and Table 40.

5.1.2.1 *Prescriber factors*

These reviews and studies confirmed most prescriber determinants identified in Belgian studies, i.e. age of GPs and time in practice, gender, professional training, perception of patient demand for antibiotics, uncertainty and fear in terms of diagnosis and prognosis, time per patient and consultation rates (Table 37).

The influence of previous clinical experience and the association between years in practice and higher antibiotic prescription was described in at least nine studies.^{156, 187} In three studies, male GPs prescribed more than female GPs.^{156, 196} There was a trend towards more inappropriate prescription among GPs compared to other specialisations when paediatric patients were studied, but results of studies from different countries were also contradictory.¹⁵⁶ In some studies, junior physicians or those in training were less confident about antibiotic prescribing, had less knowledge, and were strongly influenced by the antibiotic prescribing behaviour of the supervising physician.^{188, 208}

Studies from other countries also suggest that GPs overestimate the degree of expectations of their patients, which is often inferred by the clinician based on patient/parent description of symptoms and signs.¹⁹¹ The influence of consultation time is also related to the perception that it is time consuming to change patient beliefs and expectations:¹⁸⁸ in health systems where GPs have limited time per patient, they tend to respond to the patient demands by prescribing antibiotics rather than providing explanations why these are not needed. Several studies have shown that improvement in communication between physicians and patients can reduce patient demand for antibiotics (see section 6.1).^{193-195, 199}

Additional determinants that were identified in other studies were medical knowledge about infections and AMR, the day of the prescription, the type of practice, other factors related to the attitude of prescribers (Table 37). The two broader reviews concluded that physician's socio-demographic factors do not exert much influence but that prescriber attitude is the major factor.^{156, 187} The attitudes are categorized in two reviews and include:^{156, 187} the complacency to fulfil patients' expectations for antibiotics, the lack of confidence when prescribing (that is more frequent in young prescribers), the indifference towards the consequences of non-prudent prescription of antibiotics, the belief that the others generate AMR (other physicians, patients, the animal sector) and the fear of losing patients to competitors, which is usually caused by an overestimation of the patient dissatisfaction caused by not prescribing.



Table 37 – Determinants for antibiotic use related to the prescriber

Determinant	Association with higher prescription rates	Sources (number of primary studies if review)
<i>Determinants related to the prescriber</i>		
Age	Practice with GP > 45 years	Lopez-Vazquez et al., 2012 (8 studies), ¹⁵⁶ PHE, 2015, ¹⁸⁹ Wang et al., 2009, ¹⁹⁶ Kozyrskyj et al., 2004. ¹⁹²
Previous clinical experience and years of practice	Longer time of practice GP in first year of practice	Lopez-Vazquez et al., 2012 (9 studies), ¹⁵⁶ Teixeira et al., 2013 (9 studies), ¹⁸⁷ PHE, 2015, ¹⁸⁹ Akkerman et al., 2005, ¹⁹⁰ Cadieux et al., 2007, ²⁰⁰ Mol et al., 2004, ¹⁹⁷ Md Rezal et al., 2005. ¹⁸⁸
Gender of GP	Practices with higher % of male GPs	Lopez-Vazquez et al., 2012 (2 studies), ¹⁵⁶ PHE, 2015, ¹⁸⁹ Wang et al., 2009. ¹⁹⁶
Training, specialty, status	Non-paediatrician specialists, not being a GP trainer, negative influence of senior doctor	Lopez-Vazquez et al., 2012 (9 studies), ¹⁵⁶ Texeira et al., 2013 (5 studies), ¹⁸⁷ PHE, 2015, ¹⁸⁹ Akkerman et al., 2005, ¹⁹⁰ Kozyrskyj et al., 2004, ¹⁹² Livorsi et al., 2015. ²⁰⁸
Type of practice	Single practices, out-of-hours consultations	PHE, 2015, ¹⁸⁹ Wang et al., 2009. ¹⁹⁶
Perceived time per patient, consultation rates, size of practice, timing	Limited perceived time available, shorter duration, high volume of practice, high consultation rate, WE or holidays	Teixeira et al., 2013 (11 studies), ¹⁸⁷ PHE, 2015, ¹⁸⁹ Akkerman et al., 2005, ¹⁹⁰ Wang et al., 2005, ¹⁹⁶ Cadieux et al., 2007, ²⁰⁰ Horwood et al., 2016. ²⁰⁶
Day of the week of the prescription (Fridays)	More antibiotic prescribed on Fridays than the average of the other week days	PHE, 2015, ¹⁸⁹ van Buul et al., 2014. ²¹⁰
Communication model or skills	Lack of (time for) communication to reduce patient demand on antibiotics, poor communication	Teixeira et al., 2013 (11 studies), ¹⁸⁷ PHE, 2015, ¹⁸⁹ Md Rezal et al., 2015, ¹⁸⁸ Stivers et al., 2003, ¹⁹⁵ Cadieux et al., 2011. ¹⁹⁹
Perception that patients want antibiotics	Perception that patients/parents want AB ^o	PHE, 2015, ¹⁸⁹ Akkerman et al., 2005, ¹⁹¹ Ciofi degli Atti et al., 2006, ¹⁹⁸ Stivers et al., 2003, ¹⁹⁵ Coenen et al., 2013. ¹⁷⁰
Complacency (to fulfil patients' expectancy)	High complacency to patient demand	Lopez-Vazquez et al., 2012 (14 studies), ¹⁵⁶ Teixeira et al., 2013 (21 studies), ¹⁸⁷ PHE, 2015, ¹⁸⁹ Md Rezal et al., 2015. ¹⁸⁸
Medical knowledge of the clinician	Lack of knowledge about RTI and on AMR tests	Teixeira et al., 2013 (11 studies), ¹⁸⁷ Akkermann et al., 2005, ¹⁹⁰ PHE, 2015, ¹⁸⁹ Mol et al., 2004, ¹⁹⁷ Cadieux et al., 2011. ¹⁹⁹
Confidence when prescribing	Lack of confidence	Teixeira et al., 2013 (8 studies), ¹⁸⁷ Schouten et al., 2007, ²⁰¹ Md Rezal et al., 2015. ¹⁸⁸
Prescriber involvement in prudent AB use	Indifference to problem of AB prescribing	Lopez-Vazquez et al., 2012 (2 studies), ¹⁵⁶ Teixeira et al., 2013 (9 studies). ¹⁸⁷
Responsibility of others	Belief that others (physicians, patients) generate AMR	Teixeira et al., 2013 (6 studies), ¹⁸⁷ PHE, 2015, ¹⁸⁹ MdRezal et al., 2015. ¹⁸⁸
Fear, uncertainty of the diagnosis and prognosis	Fear of disease progression, desire for quick fix	Lopez-Vazquez et al., 2012 (7 studies), ¹⁵⁶ Teixeira et al., 2013 (15 studies), ¹⁸⁷ PHE, 2015, ¹⁸⁹ Horwood et al., 2016, ²⁰⁶ Livorsi et al., 2015, ²⁰⁸ Md Rezal et al., 2015. ¹⁸⁸
Fear of losing patients to competitors	Overestimation of patient dissatisfaction caused by not prescribing	Teixeira et al., 2013 (10 studies). ¹⁸⁷

^o: According to the literature, GPs overestimate the degree of expectations of their patients,^{170, 195, 198} AB: antibiotic(s); AMR: antimicrobial resistance; PHE: Public Health England; RTI: respiratory tract infection; GP: General Practitioner.



5.1.2.2 Factors related to the health care system

The organization of the health care system is also found to be associated with the amount of antibiotics used. Factors of the health care system that are associated with antibiotic prescription were the availability of rapid (near patient) diagnostic tests such as CRP and procalcitonin, the availability of guidelines, patient volume and the workflow of the health care system related to the lack of time for communication with the patient and determining treatment and prophylaxis, the fee for service system for GPs, and financial incentives (Table 38). The two first factors are related to potential interventions and their evaluation is further discussed in section 6.1.

The relationship between GPs and patients was also reported as a significant factor in several studies. For instance, in countries where patients are obliged to register with a GP and cannot easily consult another GP, antibiotic use is lower than in countries where this is not the case.²¹²

A study of 1998-99 data in 15 EU countries found that the number of antibiotic trade names in a country was positively correlated with the antibiotic use in the ambulatory sector (correlation coefficient 0.56).²⁰⁴ However in a more recent study using 1999-2007 data from 29 EU countries, a lower number of different antibiotic products for sale in the pharmacy was associated (in multivariate analysis) with a higher antibiotic use, though the strength of the association was low (OR=0.99 and statistically significant).²¹²

Countries with a higher proportion of gross domestic product spent on health care also use more antibiotics.²¹²

Table 38 – Determinants for antibiotic use related to the health care system

Determinant	Association with higher prescription rates	Sources (number of primary studies if review)
Payment system for GP	Fee for service predominating	Horwood et al., 2016; Murphy et al., 2011, Yuan et al., 2017. ^{206, 214, 215}
Access to diagnostic services	Lack of near-patient testing e.g. CRP and procalcitonin (See section 6.1)	Teixeira et al., 2013 (1 study). ¹⁸⁷
Policy and guidelines available	Lack of guidelines for RTI (See section 6.1)	Teixeira et al., 2013 (7 studies), ¹⁸⁷ Blommaerts et al., 2014. ²¹²
Pressure of time, workflow in hospitals	Lack of time for determining prophylaxis and for communicating with patients	Teixeira et al., 2013 (11 studies), ¹⁸⁷ PHE, 2015, ¹⁸⁹ Lopez-Vazquez et al., 2012 (7 studies). ¹⁵⁶
Number of different antibiotics available	Higher number of trade names of oral antibiotics in one study, lower number of antibiotic products in a more recent study (OR=0.99)	Monnet et al., 2005, ²⁰⁴ Blommaert et al., 2014. ²¹²
Financial incentives	(See section 6.1)	Teixeira et al., 2013 (2 studies), ¹⁸⁷ Borg, 2014. ¹⁵⁹

CRP: C-Reactive Protein ;GP: General Practitioner; OR: Odds Ratio; RTI: Respiratory Tract Infection; PHE: Public Health England.



5.1.2.3 Patient factors

As determinants for patients and parents of (young) patients found in the literature were similar, we grouped both categories in this section and in Table 39.

The literature review confirmed most of the patient/parent determinants that were identified in the studies that included Belgian subjects (Table 39): age, gender, region, socio-economic status, education, patient fear and anxiety, perception and attitude towards disease, knowledge about antibiotics and infections, vulnerability and risk factors of the patient, and demand for antibiotics. However, other age and gender groups were more likely to receive antibiotics in those studies than those described in Belgian studies (see above): in most studies, older children were more likely to receive antibiotics compared to younger ones, as well as older adults. A qualitative study highlighted that both prescribers and parents perceived children as being particularly vulnerable and this could influence antibiotic prescription.²⁰⁹

The geographical determinants revealed an East-West and South-North gradient, which may also be related to different cultural dimensions. The lack of knowledge and understanding of the public towards antibiotic resistance is still high: in the 2016 Eurobarometer survey, only 29% of Belgian respondents answered correctly to all four questions related to the knowledge of antibiotics (see section 4.3.1.6).⁵³ The attitude towards disease and the self-healing ability of the body is also influential: persons with a tendency to consult a medical doctor tended to use more antibiotics.^{157, 187} This was also related to the patient fear for severe disease and the desire for a quick fix. These last individual characteristics are also related to the cultural dimensions of a country, i.e. uncertainty avoidance and masculinity, which are described below.

5.1.2.4 Environmental and cultural determinants at country level

A number of environmental determinants of antibiotic use are described, such as season (e.g. winter) and relative humidity, as these may be related to a higher burden of influenza and other respiratory infections (Table 39).^{189, 212, 213}

The review on cultural determinants cites the two international studies that included Belgium and confirmed that Hofstede's cultural dimensions such as low distance to power, uncertainty avoidance and masculinity are correlated with antibiotic use.^{157, 158, 177} When these dimensions score high, antibiotic prescription is seen as a sign of power and expertise, decreases GPs' and patients' fear linked with uncertainty of diagnosis and outcome and meet the priority of continuing to work in spite of illness.¹⁵⁷ The influence of these factors on the communication between the practitioner and the patient is also reported. The review concluded that cultural factors have an influence on all the different stages of the disease process, from the first symptoms experienced by the patient to the decision by the practitioner to prescribe antibiotics and on treatment adherence by the patient.¹⁵⁷

The degree of corruption in the health sector and in the society in general was found to be associated to antibiotic prescription in at least two studies.^{205, 207} An EU study conducted a multivariate analysis of the variation of antibiotic resistance in 29 European countries and found that corruption is the main socioeconomic factor that explains antibiotic resistance, and was better correlated to resistance rates than antibiotic use.²¹⁶ In addition, in countries where a larger proportion of inhabitants indicated that they distrust other people, more antibiotics are used.²¹²

Other factors are the higher morbidity at population level and the overall level of school education in a country.^{196, 205, 212}



Table 39 – Determinants for antibiotic use related to the patient and its environment

Determinant	Association with higher prescription rates	Sources (number of primary studies if review)
<i>Determinants related to the patient or parent (individual characteristics)</i>		
Age and gender	Older children vs. younger children Older adults Males > females	Teixeira Rodrigues et al., 2013 (3 studies), ¹⁸⁷ Kozyrskyj et al., 2004, ¹⁹² Akkerman et al., 2005, ¹⁹¹ Mangrio et al., 2009. ²⁰²
Geographical region, North – South gradient	South vs. North and East vs. West Europe, related to awareness of AMR; other country gradients.	Touboul et al., 2015, ¹⁵⁷ citing Grigoryan et al., 2007, ²¹⁷ PHE, 2015, ¹⁸⁹ Goossens et al., 2005, ²¹³ Wang et al., 2009. ¹⁹⁶
Socio-economic factors	Economic stress / lower income of parents Poor socio-economic conditions Low ability of the parent to recognise worsening illness (as assumed by clinicians)	Teixeira et al., 2013 (4 studies), ¹⁸⁷ PHE, 2015, ¹⁸⁹ Mangrio et al., 2009, ²⁰² Kozyrskyj et al., 2004, ¹⁹² Kumar et al., 2003, ²⁰³ Cabral et al., 2015. ²⁰⁹
Education of patient/ parent	Lower maternal education in parents	Teixeira et al., 2013 (2 studies), ¹⁸⁷ PHE, 2015, ¹⁸⁹ Mangrio et al., 2009. ²⁰²
Patient knowledge on antibiotics and infection	Poorer knowledge of antibiotics (public does not understand resistance)	Touboul et al., 2015, ¹⁵⁷ (citing Deschepper), ¹⁷⁷ Borg, 2012, ¹⁵⁸ PHE, 2015. ¹⁸⁹
Risk factors and patient vulnerability	Comorbidity, pregnancy, specific condition, low birth weight, allergy, not breastfed at all	Teixeira et al., 2013 (5 studies), ¹⁸⁷ Mangrio et al., 2009. ²⁰²
Perception and attitude towards disease	Tendency to consult medical doctor, desire of quick fix	Touboul et al., 2015 (5 studies) ¹⁵⁷ Teixeira et al., 2013 (4 studies). ¹⁸⁷
Demand for antibiotics	High patient demand or hope for antibiotics	Kumar et al., 2003, ²⁰³ Coenen et al., 2013. ¹⁷⁰
Fear / anxiety, level of social support	Fear of severe disease, anxious parents, feeling the risk of threat, low emotional support of parents	Teixeira et al., 2013 (2 studies), ¹⁸⁷ Mangrio et al., 2009, ²⁰² Horwood et al., 2016, ²⁰⁶ Cabral et al., 2015. ²⁰⁹
<i>Determinants related to the patient environment</i>		
Season	Winter season	Goossens et al., 2005, ²¹³ PHE, 2015, ¹⁸⁹ Kozyrskyj et al., 2004. ¹⁹²
Relative humidity	Higher humidity country	Bloomaerts et al., 2014. ²¹²
<i>Other determinants related to the patient country (besides health care system and environment)</i>		
Distance to power	Population with low distance to power	Touboul et al., 2015, ¹⁵⁷ Deschepper et al., 2013. ¹⁷⁷
Uncertainty avoidance*	Country with high uncertainty avoidance	Touboul et al., 2015, ¹⁵⁷ Borg, 2014, ¹⁵⁹ Deschepper et al., 2008, ¹⁷⁷ Gaygisiz et al., 2017. ²⁰⁵
Masculinity vs. femininity*	Society with high 'masculinity' culture, including result oriented and 'live to work' ethics	Touboul et al., 2015, ¹⁵⁷ Borg, 2014, ¹⁵⁹ Deschepper et al., 2008, ¹⁷⁷ Gaygisiz et al., 2017. ²⁰⁵
Corruption and governance quality**	High index of corruption in health sector and in society**	Rönnerstrand et al., 2017, ²⁰⁷ Gaygisiz et al., 2017. ²⁰⁵
Feelings of distrust	Country with high feeling of distrust	Bloomaerts et al., 2014. ²¹²
Educational level at country level	Low mean years of schooling in country	Gaygisiz et al., 2013. ²⁰⁵

*: according to Hofstede's cultural dimensions; **: according to interviews on the prevalence of corruption in the health sector and prevalence of bribes in the society and/or the indicator 'control of corruption' from the International Country Risk Guide developed by the Political Risk Services Group or indicators of the Worldwide Governance Indicators (WGI) database from the World Bank (<http://info.worldbank.org/governance/wgi/index.aspx#home>). Those studies used either all dimensions of governance quality or the 'Control of Corruption' indicator, which measures the extent to which public power is applied for private gain. AMR= Antimicrobial Resistance.



5.1.2.5 Determinants of antibiotic prescription in nursing homes

Only few studies assessed the determinants of antibiotic use in long-term health care facilities (LTCF), such as nursing homes. Many studies focused on the patient clinical picture, and some date from the nineties.^{143, 210, 211, 218-220} The European point prevalence surveys conducted in LTCF in 2016-17 (Healthcare-Associated infections in Long-Term care Facilities or HALT, see section 4.2.1.2) showed that antibiotic use was higher in males and older subjects (>85 years), in those using a wheelchair or bedridden as well as in those with other clinical risk factor such as vascular catheter.¹⁴³ Antibiotic use was also higher in smaller nursing homes compared to large ones.¹⁴³ Older studies report that the majority of prescriptions were made by phone order and/or without examination of the patient.^{218, 219} A qualitative study in long-term care facilities in the Netherlands retrieved some of the same determinants as those described for ambulatory care: diagnostic uncertainty, risk avoidance ('better safe than sorry'), influence of peers, pressure from the family and days of the week (i.e. Fridays).²¹⁰ The diagnostic uncertainty is aggravated in LTCF by the lack of on-site diagnostic resources such as laboratory and X-Ray and the impaired communication with LTCF patients. A large study in Canada among 67 000 long-term care residents reports that long antibiotic duration course was not associated with patient characteristics but with the individual prescriber's profile ('prescriber preference').²²⁰ This corroborates the results of an older Belgian study in general ambulatory care.¹⁶⁸

5.1.3 Determinants of antibiotic use by patients

Other elements that influence the use of antibiotics in the Belgian population relate to the patient behaviour:

- adherence to the prescribed treatment, also called compliance in some studies, and
- self-medication, or auto-medication, i.e. intake of antibiotics that were not prescribed for that episode.

The over-the-counter use being very rare in Belgium, that element is not addressed here. The literature search was limited to studies that included Belgium or multi-country studies that included several European countries.

The adherence to anti-TB treatment or to other long-term treatment was excluded. We did not retrieve data on symptoms and clinical signs. The determinants of adherence to antibiotic treatment and self-treatment are described in Table 40.

Determinants for treatment adherence and self-medication vary across countries. Overall, studies report that the relationship between antibiotic prescribing and antibiotic use is not clearly understood.²²¹

5.1.3.1 Adherence or compliance to antibiotic treatment

Once antibiotics are prescribed they must also be correctly used by the patient. Adherence has been defined as 'the process by which patients take their medicine as prescribed'.^{222, 223} Different processes are involved in patient adherence: treatment initiation, implementation and discontinuation.²²²

No Belgian study assessing the determinants of adherence to antibiotic treatment was found, except for a 2001 observational study that compared compliance to two drug regimens in Namur.²²⁴ Five studies were retrieved: three multi-country studies including Belgian data, one systematic review and one multi-country study involving European countries.^{221, 222, 225-227}

Their characteristics are described in Table 55 (see Appendix 1.1). Definitions and methods to measure adherence varied across studies,²²⁷ and non-adherence is usually based on self-reporting.

Overall, the adherence to antibiotic treatment in Belgium was relatively high compared to other EU countries.²²⁵ A global survey reported in 2001 that 69% of the patients who had an antibiotic treatment prescribed claimed to have taken the course until the end, and this proportion varied from 53% to 90% among included countries.²²⁵ Among the approximately 600 Belgian interviewees, 82% claimed to have finished the course of antibiotics and 13% saved part of the course for future use.²²⁵ A follow-up study reported that reasons for non-compliance also varied with the countries.²²⁶ Interviewees also reported that it was possible to get antibiotics from the pharmacist without prescription in Belgium (the study was published in 2001), even though it was and still is illegal. A 2015 trial involving Belgian patients of GP practices estimated an overall adherence at 88% to a 7-days amoxicillin treatment for lower respiratory tract infection (LRTI).²²⁸



Adherence tends to be highest for RTI and lowest for genitourinary tract infections (GUI) and acute diarrhoea according to a 2005 systematic review.²²⁷

The determinants identified in the retrieved studies also depend on the type of data collected, but included (Table 40): age, long duration of symptoms before consulting a doctor, longer treatment duration, feeling better, attitudes to doctors and patient type (personality traits) and country with more single-handed practice (for discontinuation of treatment). The influence of age is unclear: in some studies, adherence was lower in studies of adults than in studies of children,²²⁷ and in other studies, older adults were more compliant to treatment.²²² In the three GRACE studies (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe), one showed a higher adherence (not significant) in older age and the two others showed the opposed relationship.²²² A study on personality traits and attitude to doctors classified the type of patients, and reported that two patient types are more likely to be non-compliant to the treatment: 'critical' patients i.e. doubting about physician competence and 'ignored' patients i.e. having poor interaction with physician and not feeling believed.²²⁶ Two publications from the GRACE initiative among EU countries suggested that individual clinician factors play a limited role in influencing adherence.^{221, 222}

The influence of the number of antibiotic intakes per day is debated. This was identified as a determinant of treatment adherence in a number of studies.^{226, 229, 230} However, this was not observed in a more recent multi-country study that included Belgium,²²¹ neither in a Dutch trial in which compliance was high for both, once or three times daily antibiotic intake (98% and 91%, respectively).²³¹ A 2015 meta-analysis of 26 studies in industrialised countries revealed a slightly higher (9%) compliance of a once-daily regimen in adults compared to a multiple times daily regimen (RR=1.09; 95% CI 1.02-1.16).²³² Compliance was 10% higher in children receiving an antibiotic twice daily compared to those receiving the same antibiotic thrice-daily (RR=1.10; 95% CI 1.02-1.19).²³² However, the higher compliance was mostly observed in older studies and was rarely significant in studies published after 2000.



Table 40 – Determinants for antibiotic adherence and self-medication

Determinant	Association with non-adherence to treatment or with self-medication	Sources
<i>Determinants related to patient adherence</i>		
Prior duration of symptoms	Duration >28 days before consulting (duration <7 days less likely to initiate)	Francis et al., 2012, ²²¹ Gillespie et al., 2017. ²²²
Treatment duration	Long course duration (>5 or >8 days)	Francis et al., 2012, ²²¹ Gillespie et al., 2017. ²²²
Age	Adults vs. children Older adults were more compliant	Kardas et al., 2005, ²²⁷ Gillespie et al., 2012. ²²²
Subjective feeling	Feeling better	Pechere et al., 2001. ²²⁵
Attitudes to doctors and patient personality traits	'Critical' and 'ignored' patient types	Pechere et al., 2007. ²²⁶
Health care setting for PHC	Countries where single-handed practices are widespread	Gillespie et al., 2017. ²²²
<i>Determinants related to self-medication</i>		
Age	Younger age	Grigoryan et al., 2006. ²³³
Education	Higher education level	Grigoryan et al., 2006, 2008 and 2007. ^{217, 233, 234}
Country wealth	Lower GDP per capita (low association)	Grigoryan et al., 2008. ²³⁴
Co-morbidity	Presence of a chronic disease	Grigoryan et al., 2008. ²³⁴
Symptoms	URTI in general, red or sore throat, bronchitis, UTI, toothache	Grigoryan et al., 2007 and 2008. ^{217, 234}
Having been previously prescribed antibiotics and availability of left-overs	Prescribed use for URTIs associated with self-medication by leftover, OR=15.7 in low and 8.6 in high education	Grigoryan et al., 2007, ²¹⁷ Kardas et al., 2007 ²³⁰
Antibiotic dispensing system	Pack-based dispensation system (OR 0.51 for exact number)	Grigoryan et al., 2008. ²³⁴
Knowledge about antibiotics	Incorrect knowledge on effect of antibiotics on bacteria and viruses*	Grigoryan et al., 2008. ²³⁴
Awareness about ABR	Non-awareness about ABR	Grigoryan et al., 2008. ²³⁴
Attitude towards minor ailment	Favouring AB use for minor ailment (OR 1.8)	Grigoryan et al., 2008. ²³⁴
Power distance	Low distance to power	Deschepper et al., 2008. ¹⁷⁷

ABR: antibiotic resistance; GDP: gross domestic product; OR: Odds Ratio; UTI: Urinary Tract Infection; URTI: Upper Respiratory Tract Infection; *: non-significant.



Determinants identified in other recent studies from European countries (Spain, Portugal, Sweden) confirmed the above identified determinants, in particular older age, treatment duration, relationship with the physician, feeling better and personality traits.²³⁵⁻²³⁷

It should be noted that 10% of Belgian respondents do not know when they can stop an antibiotic treatment, compared to an EU average of 15%, according to the 2016 Eurobarometer.⁵³

5.1.3.2 Self-medication

A total of six studies on determinants for self-medication and including Belgian subjects or data were retrieved.^{177, 217, 230, 233, 234, 238} Results are dominated by one large multi-country EU study which is analysed in four papers: two publications describe sub-analyses and two others were a follow-up study.^{217, 233, 234, 239}

In the 2016 Eurobarometer, only 5% of Belgian respondents did not obtain their last course of antibiotics from a medical practitioner, compared to 7% for the whole of the EU (see Table 11 in section 4.3.1.4).⁵³ In two older studies, Belgian interviewees saved part of the last antibiotic treatment for future use at home and expressed that they did or could use these antibiotics for other disease episode.^{169, 225} In northern and western EU countries, the major source of antibiotic self-medication was leftover medication (44%).²³³ Indeed prescribed antibiotics were strongly associated with self-medication from leftovers, and the association was higher in participants from lower level of education, OR=15.7 (95%CI 6.1-40.4) for low education and OR=8.6 (95% CI 3.7-20.1) for high education.²¹⁷ Other determinants identified in the studies involving Belgian subjects were: younger age, higher educational level, presence of a comorbidity, incorrect knowledge about antibiotics (though not significant), non-awareness about antibacterial resistance, pack-based dispensation system compared to dispensing the exact number of tablets in pharmacies, and personal attitude to use antibiotics for minor ailment.^{233, 234} At a country level, self-medication was associated with a lower country GDP and a low distance to power (as cultural dimension).^{177, 234}

A EU study, not including Belgium, concluded that the strongest predictors for the possession of antibiotic leftovers in the ambulatory sector were living in a country where antibiotics are dispensed in fixed packs, such as in Belgium, rather than in exact numbers of pills, as well as believing that leftover antibiotics can be saved and used again.²³⁰ This issue is further discussed in section 8.2.

5.1.4 Limitations

The methodology of studies on determinants of antibiotic use is very heterogeneous. The quality of studies is considered as poor overall by two of the systematic reviews.^{156, 157} A number of studies look at the quantitative association between a variable and prudent antibiotic prescription and of these use the rate of antibiotic prescription as a proxy for prudent use. A few studies are based on fictitious cases in order to simulate prescribing, using questionnaires, focus groups or face-to-face interviews with GPs, assuming that only prescriber's knowledge is influencing prescription.¹⁵⁶ In some qualitative studies, a motive to prescribe antibiotics expressed by one participant may be described as a determinant while the association with antibiotic use was not assessed, although qualitative studies are rather meant to be exploratory tools to identify potential determinants.

A number of studies have used the Hofstede cultural dimensions to describe determinants related to the country cultural characteristics, and these have many opponents. Some authors debate on the conceptual aspects of Hofstede cultural dimensions, such as do national cultures exist, can culture be measured and can country cultures be summarized in scores.^{240, 241} The methodology has also been criticized e.g. for using small sample sizes, for respondents – all belonging to one company IBM – not being representative for a country.²⁴¹



Key messages

- Determinants (or factors) that influence prudent antibiotic prescription and use are overall the same in studies including Belgian subjects and those from other countries. Determinants are individual factors related to the prescriber or to the patient, or broader factors related to the country health care system and the culture (identified by international studies comparing countries).
- Prescriber factors that were consistently associated with higher antibiotic prescription are using the fee for service system, the uncertainty related to disease diagnosis and outcome (which is more prevalent in a GP setting), time pressure and the need for 'rapid fix'.
- Physicians tended to prescribe more easily (unnecessary) antibiotics to patients or parents of patients who were anxious, who consulted their GP more often, who needed a medical note for a sick leave and who were perceived as more vulnerable according to disease severity and socio-economic status. GPs prescribed more easily antibiotics to patients whom they perceived as wanting antibiotics, but they overestimated the patient demands for antibiotics.
- Residing in Wallonia (for the patient and/or the prescriber) is associated with higher use of antibiotic compared to residing in Flanders. Qualitative studies in Wallonia revealed a lack of confidence in guidelines among GPs.
- Factors of the Belgian health care system favouring antibiotic prescription are the high consultation rates, the fee for service system and the low access to rapid (near patient) diagnostic tests.
- Cultural factors favouring antibiotic prescription include uncertainty avoidance, low distance to power, i.e. patients do not feel very involved in medical decisions, and societies with a 'live to work' ethic.

- Limited data were found on the determinants of antibiotic prescription and use in nursing homes. The low access to diagnostic resources and the impaired communication with patients are likely to aggravate the high antibiotic prescription.
- These findings suggest that simply copying strategies from other organisations of health care (e.g. from the Netherlands) will not be sufficient to improve antibiotic use in Belgium due to cultural differences. In other words, importing solutions from abroad is no guarantee for success.

5.2 Determinants of antibiotic prescription and choice in veterinary medicine

In the following chapter we provide an overview of the determinants of antibiotic prescribing and choice in veterinary medicine.

5.2.1 Methods

On 16 October 2017, a literature search in Medline was done in order to identify scientific articles on the determinants of antibiotic prescription and use in the European veterinary sector, covering the period 2007-2017. The search strategy is provided in Appendix 2.1.

The search resulted in 275 references, however after selection based on title, abstract and full text, only 17 references were retained. Position papers (n=2), clinical studies (n=148), studies on frequency of prescribing (n=21), antibiotic sales (n=5), antibacterial resistance (n=21), guidelines (n=3), disease outbreaks (n=1), antibiotic use in human medicine (n=22), antibiotic use in very specific animal species (e.g. laboratory animals, mink) (n=4), studies from outside Europe (n=25), and studies reporting in another language than French, Dutch or English (n=6) have been excluded. An additional 3 references were found through snowballing and desk research (see Figure 41 in Appendix 2.1).

Included studies are diverging in type of research and number of respondents. All studies are observational, some used quantitative (e.g. surveys) and others qualitative research techniques (e.g. interviews, focus



groups). The latter are more exploratory in character and have fewer participants (n= 11 up until 24).

Note that antibiotics can be used in several ways in the veterinary sector; they are described in Box 22.

Box 22 - Definitions of treatment types

Group treatment: prophylactic, metaphylactic or therapeutic administration of medication to a couple of animals, either through parenteral or through oral route (feed or water).

Prophylactic treatment: the administration of a medicinal product to an animal or group of animals before clinical signs of a disease, in order to prevent the occurrence of disease or infection treatment of a group of animals at strategic moments in the production cycle (e.g. piglets after weaning) in order to prevent an infection resulting in sick animals and or decreasing production results. Prophylactic treatment will be phased out in Europe by 2022.²⁴²

Metaphylactic treatment: the administration of a medicinal product to a group of animals after a diagnosis of clinical disease in part of the group has been established, with the aim of treating the clinically sick animals and controlling the spread of the disease to animals in close contact and at risk and which may already be subclinically infected.

Therapeutic treatment: treatment of an infected animal or a group of infected animals showing clinical symptoms.

Source: *Prudent use of antibacterial agents in group treatment of farm animals and the effect on resistance selection*, FAVV – AFSCA, 2013.²⁴³

5.2.2 Determinants of antibiotic prescription

Several authors have listed influential determinants in antimicrobial prescribing behaviour of farm animal veterinarians. In general, examples are: the belief in the professional obligation to alleviate animal suffering, financial dependency on clients, risk avoidance, advisory skills, financial barriers, contribution to antimicrobial resistance and major economic powers.²⁴⁴ In addition, two multivariate models have been made explaining prescribing behaviour: one for food-producing animals and one for companion animals.

In 2017, a model integrating both qualitative and quantitative research efforts regarding antibiotic use in the sector of food-producing animals has been published.²⁴⁵ It combines intrinsic motivating and enabling factors to explain the uptake of antibiotic reduction practices.²⁴⁵ Enabling factors are the influence of the agricultural community and industry, the influence of society, and resources such as knowledge, skills, time and budget. The intrinsic motivating factors are the attitude^{pp} towards antibiotic reducing practices, normative beliefs^{qq} about antibiotic reducing practices and the perceived behavioural control^{rr} (ability beliefs) of veterinarians and farmers. These three motivating factors determine the intention to take preventive measures or antibiotic reducing practices and are mediated by the enabling factors.²⁴⁵

Similarly an overview of intrinsic and extrinsic factors influencing decision-making on antibiotic use in small animal practices has been made. Clearly antimicrobial usage was determined not only by clinical evidence and scientific knowledge, but also by factors such as preferences and previous experiences, perceived efficacy, ease of administration, perceived compliance and cost of therapy.²⁴⁷

^{pp} Attitude: the degree to which the person has a favourable or unfavourable evaluation of the behaviour in question.²⁴⁶

^{qq} Normative beliefs: the influence of social pressure that is perceived by the individual (*normative beliefs*) to perform or not perform a certain behavior.²⁴⁶

^{rr} Perceived behavioural control: the individual's belief concerning how easy or difficult performing the behaviour will be.²⁴⁶



Table 41 lists all determinants of veterinary antibiotic prescription and use found in the literature. Studies reporting the perspective of veterinarians and/or farmers are further developed below.

Table 41 – Determinants of veterinary antibiotic prescription and use

Determinant	Source
Agricultural factors (e.g. housing, feeding systems)	Coyne et al., 2014 ²⁴⁸
Animal age	Mateus et al., 2014 ²⁴⁷
Animal body weight	Mateus et al., 2014 ²⁴⁷
Animal species and associated behaviour	Mateus et al., 2014 ²⁴⁷
Attitudes of senior and junior veterinarians towards AB use	Mateus et al., 2014 ²⁴⁷
Attitudes, risk perception and aversion	Speksnijder, 2017 ²⁴⁵
Awareness of recommendations for responsible AB use	Mateus et al., 2014 ²⁴⁷
Capacity of veterinarian to elicit farmers' true goals and beliefs and to tailor advices to this knowledge base	Speksnijder, 2017 ²⁴⁵
Client pressure and dependency	Speksnijder et al., 2015a ²⁴⁴ ; Coyne, et al., 2016 ²⁴⁹ ; Coyne et al., 2014 ²⁴⁸ ; Speksnijder et al., 2015b ²⁵⁰
Client pressure and expectations	Mateus et al., 2014 ²⁴⁷ ; Coyne et al., 2014 ²⁴⁸ ; Hughes et al., 2013 ²⁵¹
Clinical signs	Mateus et al., 2014 ²⁴⁷ ; Hughes et al., 2013 ²⁵¹
Competition between veterinarians	Speksnijder, 2017 ²⁴⁵
Confidence in own knowledge regarding disease prevention	Speksnijder, 2017 ²⁴⁵
Conflicting advices to farmers	Speksnijder, 2017 ²⁴⁵
Cost of therapy, financial constraints	Mateus et al., 2014 ²⁴⁷ ; Hughes et al., 2013 ²⁵¹
Degree of integration^{ss} and integration size	Pardon et al., 2012 ²⁵²
Diagnostic tests	Mateus et al., 2014 ²⁴⁷ ; Hughes et al., 2013 ²⁵¹
Differing views on the indications for prescribing AB	Coyne, et al., 2016 ²⁴⁹ ; Coyne, et al. 2014 ²⁴⁸
Drug availability	Mateus et al., 2014 ²⁴⁷ ; Coyne et al., 2014 ²⁴⁸
Drug efficacy	Coyne et al., 2014 ²⁴⁸
Drug sales and veterinary pharmacy	Speksnijder et al., 2015a ²⁴⁴ ; Coyne, et al., 2016 ²⁴⁹
Duration of AB therapy	Mateus et al., 2014 ²⁴⁷
Effectiveness of AB use written protocols	Mateus et al., 2014 ²⁴⁷

^{ss} An integration is defined as a company that combines all steps of the production chain by having its own feed plant and slaughterhouse and by placing its calves in veal herds owned by producers that fatten the calves for this company according to a contract.²⁵²



Determinant	Source
Farmers' past experiences	Speksnijder, 2017 ²⁴⁵
Financial barriers for structural veterinary herd health advisory services	Speksnijder et al., 2015a ²⁴⁴
Financial dependency on clients/farmers	Speksnijder et al., 2015a ²⁴⁴
Formulation and ease of administration	Mateus et al., 2014 ²⁴⁷ ; Hughes et al., 2013 ²⁵¹ ; Fertner et al., 2016b ²⁵³
Guidelines and guideline use	Sarrazin et al., 2017; Speksnijder, 2017 ²⁴⁵
Health status of the herd	Coyne et al., 2014 ²⁴⁸
Hierarchical structure and professional relationships	Mateus et al., 2014 ²⁴⁷
Import of pig products and pressure from retailers	Coyne et al., 2014 ²⁴⁸
Influence of staff effectiveness meetings	Mateus et al., 2014 ²⁴⁷
Knowledge of (non)infectious diseases	Mateus et al., 2014 ²⁴⁷
Lack of farmers' compliance to veterinary recommendations	Speksnijder et al., 2015a ²⁴⁴ ; Coyne et al., 2016 ²⁴⁹
Lack of collaboration between advisors	Speksnijder, 2017 ²⁴⁵
Length of consultation	Mateus et al., 2014 ²⁴⁷
Owner's experience with ABs	Mateus et al., 2014 ²⁴⁷
Organisation of the production chain and dependency on other chains	Speksnijder, 2017 ²⁴⁵
Perceived efficacy	Mateus et al., 2014 ²⁴⁷
Perceived owner compliance	Mateus et al., 2014 ²⁴⁷
Personal beliefs regarding the veterinary contribution to antimicrobial resistance	Speksnijder et al., 2015a ²⁴⁴
Personal preference of antimicrobial	Mateus et al., 2014 ²⁴⁷
Preference for broad spectrum over narrow AB's	Mateus et al., 2014 ²⁴⁷
Pressure senior veterinarians on junior colleagues	Coyne, et al., 2016 ²⁴⁹
Pressures from policy and legislation	Coyne et al., 2014 ²⁴⁸
Previous clinical history of the animal	Mateus et al., 2014 ²⁴⁷
Professional obligation to alleviate animal suffering	Speksnijder et al., 2015a ²⁴⁴
Public health interests	Speksnijder et al., 2015a ²⁴⁴
Public perception/opinion	Coyne et al., 2014 ²⁴⁸ ; Speksnijder, 2017 ²⁴⁵
Rearing system (e.g. all-in-all-out pig flow)	Coyne et al., 2014 ²⁴⁸
Regulations	Speksnijder, 2017 ²⁴⁵
Risk and uncertainty avoidance, fear of complications (of veterinarians and farmers)	Speksnijder et al. 2015a ²⁴⁴ , Speksnijder, 2017 ²⁴⁵
Shortcomings in advisory skills	Speksnijder et al, 2015a ²⁴⁴



Determinant	Source
Stocking density	Postma et al., 2015 ²⁵⁴ ; Dewulf, et al., 2006 ²⁵⁵
Stockmanship^{tt} of the farmer	Speksnijder, 2017 ²⁴⁵
Veterinarians' lacking communication and advisory skills	Speksnijder, 2017 ²⁴⁵
Veterinarian's prior experience of a drug	Gibbons et al., 2013 ²⁵⁷
Veterinarians' years of experience	Speksnijder et al. ²⁵⁰
Willingness or ability to pay AB therapy	Mateus et al., 2014 ²⁴⁷
Work experience	Mateus et al., 2014 ²⁴⁷

AB: Antibiotic

5.2.2.1 Veterinarians experience client pressure

Client pressure has been described as a potential driver for antimicrobial prescribing by veterinary prescribers.²⁴⁹ This comprises not only farmers asking or expecting antibiotic prescription, but also the blame on veterinarians should an antimicrobial not be prescribed and later prove to have been indicated.²⁴⁸ The awareness of the potential for litigation under such circumstances was identified as a possible driver for antimicrobial use.²⁴⁹

At the same time, veterinarians feel the expectation to safeguard public health sometimes conflicts with the interests of farmers.²⁴⁴ Apparently, there is international variation. A cross-national comparative study revealed that Flemish veterinarians (n=174) experience more client pressure than their Dutch colleagues (n=437): 31.9% of the Flemish respondents felt at least once in every two months forced to prescribe, while the respective proportion in the Dutch respondents was only 14.5%.²⁵⁸

In addition, age of the prescriber and years of experience relate to client pressure. Veterinarians with fewer years in practice experienced most frequently explicit pressure from their clients to prescribe antibiotics while they were not supporting this and most uncertainty to act as an independent advisor.²⁵⁰ However, these results should be interpreted with care, since more than half of the respondents reported to only feel this pressure twice a

year or less. The authors of the above study provided two explanations for their observations. First, for younger veterinarians who like to build a long lasting mutual relationship with a farmer as a client, it might feel uncomfortable to be too paternalistic towards a farmer or to refuse strong demands. Second, in general, older veterinarians are less reluctant in antibiotic prescribing, hence pressure from clients to prescribe is less required to make them prescribe. In addition, pressure is less perceived by the older veterinarians.¹⁹⁰ This latter reasoning was supported by the finding that increasing experience is associated with being less concerned to prescribe antibiotics to prevent animal diseases and with a limited awareness of the veterinary contribution to the global threat of antimicrobial resistance at the macro level.¹⁹⁰

5.2.2.2 Senior veterinarians' pressure on junior colleagues

In line with the finding that older veterinarians might prescribe antibiotics more easily, a qualitative study reports (n=21 veterinarians) that a minority of interviewees acknowledged that senior colleagues put some pressure on more junior practitioners, which was often to maintain good relationships between long-term clients and practices.²⁴⁹

^{tt} Stockmanship is the art and science of handling cattle, or any other farm animal, properly.²⁵⁶



5.2.2.3 Veterinarians' profit from drug sales

For many veterinarians drug sales contribute to their income. Hence prescribing less, runs counter to their own interest. This conflict of interest has been debated in a number of countries such as in the UK, the Netherlands and Denmark. Research on this topic however mostly puts the importance of drug sales as a driver for antibiotic use into perspective, arguing that antibiotics are too cheap to be profitable. For example in a qualitative study it was reported that pharmacy incomes from antimicrobial selling were no longer a stimulus to prescribe antimicrobials. Some respondents mentioned that pharmacy incomes from selling antimicrobials had been replaced by selling vaccines and non-steroids which they did not consider to be a threat for public health.²⁴⁴ Coyne et al. report from their qualitative study (n=21) that many interviewees felt driven to try to reduce the cost of antimicrobials for farmers and did not feel that the profit margin on an antimicrobial would motivate prescribing behaviours. Thus, the majority felt that the 'decoupling' of antimicrobial sales, whereby veterinary surgeons are no longer able to dispense drugs directly to clients, would not affect the total amount of antimicrobials used in pigs.²⁴⁹

5.2.2.4 The implementation of guidelines on antibiotic use

Numerous treatment guidelines on responsible antibiotic use have been developed by a variety of national, European and international bodies (e.g. AMCRA, European Platform for the Responsible Use of Medicines in Animals (EPRUMA) 2008, Federation of Veterinarians of Europe (FVE) 2012, World organisation of Animal Health (OIE) 2015, European commission (EC)).^{6, 259-262}

The effect of the AMCRA antibiotic guideline for companion animals on the prescription behaviour of veterinarians was evaluated in a small scale (n=14 practices) prospective study comparing first consultations of cats and dogs one month prior with consultations at least 20 days after the implementation of the guideline. The proportion of consultations where antibiotics were prescribed decreased (-12% in both cats and dogs), however, surprisingly an increase in the prescription of third-choice and highest priority critically important antibiotics was noticed in both cats (+ 8 and + 12%, respectively) and dogs (both + 5%). The most frequently cited reasons to diverge from the guidelines were practical reasons (e.g. drug not in stock), the preference for

injections instead of tablets (e.g. cefovecin in cats), good experience with other antibiotics (than the ones recommended in the guideline) for that specific condition, and declination of additional diagnostic tests by the owner, preventing to comply with the diagnostic requirements before prescribing an antibiotic.²⁶³

The difficulty of guideline implementation was also illustrated in other countries. In the UK, veterinarians working in the UK pig industry (n=21 practices) showed an awareness of guidelines on the responsible use of antimicrobials, but they were seldom implemented in veterinary practices.²⁴⁹ In the Netherlands, veterinarians (qualitative study with n=11) indicated that national treatment guidelines and summaries of product characteristics are generally leading their choice for an antibiotic. However, they deviated from formularies and product summaries based on their empirical experience and practice routines.²⁴⁴

In order to gain a better insight into the decision-making process of veterinarians in Europe when deciding which antibiotics to prescribe, the European Medicines Agencies and the Federation of Veterinarians of Europe undertook a survey in 2012, which was completed by 3 004 practitioners from 25 European countries (among which Belgium). The most frequently cited reasons for not taking into account responsible use guidelines were: easier administration (owners request a broad spectrum antibiotic with a short withdrawal period which is easy to administer); treatment initiation in the case of critically ill animals; limited choice because of a limited number of authorized medicines for minor species (e.g. rabbits), previous experiences; welfare reasons (they do not want the animal to suffer longer than is necessary); price or other economic factors; and finally, previous treatment failure.²⁵⁹



5.2.2.5 Attitudes, risk perception, risk aversion and social approval

In human medicine, the influence of attitudes, risk perception and risk aversion of medical doctors is widely acknowledged to influence antimicrobial prescribing practices, apart from rational clinical considerations.²⁶⁴ Probably the same phenomenon is at play in the veterinary sector where attitudes and risk perceptions of farmers and veterinarians probably also influence antibiotic use. Risk perception, but also social approval as explanations for antibiotic use have also been suggested by others and need further investigation.^{245, 265}

5.2.3 Determinants of antibiotic choice

A survey completed by 3 004 veterinarians from 25 European countries, revealed that, in general the most frequently cited factors governing the selection of an antibiotic are: veterinarians' own experience, the risk for antibiotic resistance developing, ease of administration and sensitivity test results. The least important factors are considered to be owner demand, culture, profit margin, and advertising.²⁵⁹

Table 42 lists the determinants we found in the literature regarding antibiotic choice. The administration route, therapy compliance, and withdrawal times are described in more detail because they are linked to the choice for critically important antibiotics.

Table 42 – Overview of determinants of antibiotic choice

Determinant	Source
Compliance	Coyne et al., 2014 ²⁴⁸
Diagnosis	McDougall et al., 2017 ²⁶⁶
Ease of administration	De Briyne et al., 2017 ²⁵⁹ ; Coyne et al., 2014 ²⁴⁸
Farmers' preference and feedback	McDougall et al., 2017 ²⁶⁶
Formulation	Coyne et al., 2014 ²⁴⁸
On-farm disease pattern	McDougall et al., 2017 ²⁶⁶
Response to previous treatments	McDougall et al., 2017 ²⁶⁶
Risk of antibiotic resistance developing	De Briyne et al., 2017 ²⁵⁹
Sensitivity test results	De Briyne et al., 2017 ²⁵⁹
Veterinarians' own experience	De Briyne et al., 2017 ²⁵⁹ ; McDougall et al., 2017 ²⁶⁶
Withdrawal period	Coyne et al., 2014 ²⁴⁸

5.2.3.1 The administration route and therapy compliance

In a qualitative study with 11 veterinarians, several respondents indicated that the administration of medicines should be as convenient as possible for the farmer to increase therapy compliance. Thus, administration route and administration interval as well as withdrawal times for slaughter or milk delivery were considered when choosing an antibiotic.²⁴⁴

In a qualitative interview study conducted with 21 veterinarians in the UK, respondents described conflict between their desire to limit the use of critically important antimicrobials as first-line choices and the desire to maximize farmer compliance. Some stated that they have used a critically important antimicrobial, due to the longer duration of action, to improve compliance and therefore ensure that the pig received the correct dose of antimicrobial.²⁴⁹ In some clinical situations veterinarians may choose a long-acting preparation of a critically important antimicrobial as a first-line option due to concern that a farmer is unlikely to administer repeat injections of an alternative short-acting antimicrobial.^{248, 249}



5.2.3.2 *The availability of products and the withdrawal period*

The use of critically important antimicrobials (see Box 21) seems to be linked to product availability and withdrawal period (see Box 23).²⁴⁸ For example there is among veterinarians great concern about Tylosin®, which is on the list of critically important antimicrobials. This was the only authorised antibiotic available as an in-feed formulation for use in pigs near slaughter because the withdrawal period is zero.²⁴⁸ Later research (qualitative interview study, n=21) from the same authors confirmed this finding.²⁴⁹

5.2.3.3 *Differentiation between veterinarians*

The determinants for prescribing antibiotic are heavily dependent on the prescribing context: they will differ for the different types of practice (e.g. small animal practice, cattle practice) and for instance withdrawal periods (see Box 23) are not relevant in companion animal practice, but are often an important determinant in the decision to prescribe in production animals.²⁶⁷ A Dutch study confirmed the differentiation in antibiotic prescription behaviour between veterinarians working with ruminants (ruminant specialists), veterinarians working with several different animal species (generalists), and veterinarians mainly working with intensively raised animals (pigs, poultry, veal calves) (intensive specialists).²⁵⁰

Box 23 – Withdrawal period

Withdrawal periods reflect the amount of time necessary for an animal to metabolize an administered product (e.g. an antibiotic) and the amount of time necessary for the product concentration level in the tissues to decrease to a safe, acceptable level, so that the presence of antibiotic residues in animal products for human consumption, such as meat, milk or eggs can be minimized. Withdrawal times depend on the medication that is given and they may be extended when combinations of drugs are used.

Source: Nisha et al., 2008.²⁶⁸

5.2.3.4 *Differentiation between clients*

Differentiation can also be expected depending on the animal sector and contextual characteristics such as the feeding and housing system. However, the literature suggests that antibiotic use may differ more between individual farms than between different rearing systems (e.g. indoor versus outdoor, slatted versus straw-based systems^{uu}).²⁶⁹

5.2.4 *Limitations*

Most qualitative studies only included small samples of veterinary doctors. In some studies determinants are identified (e.g. the pressure from farmers/clients to prescribe antibiotics), while their occurrence was really low (e.g. twice a year or less).

We are well aware of the diverging importance of the determinants. However, since many studies have a qualitative design using exploratory techniques such as interviews or focus groups, the impact or weight of each determinant relative to others is impossible to assess.

^{uu} Slatted versus straw-based housing refers to the flooring of the pens in which animals are kept. Slatted floors have mostly concrete slats, in contrast to straw-based accommodation consisting of solid concrete flooring covered with straw. For a comparison of the strengths and weaknesses of both housing systems we refer to Scott et al., 2006.²⁶⁹



Key messages

- In common with the human sector, risk and uncertainty avoidance, the belief in the professional obligation to alleviate suffering, fear of complications, patient/client pressure and expectations are important determinants for antibiotic prescribing.
- But unlike the human sector, the veterinary sector suffers from important economic pressure. An infection not well or timely diagnosed and treated, may have severe economic impact for the farmer, leading farmers to ask for antibiotics. From the veterinarians' side, the fear for being blamed and/or litigated is a driver for antimicrobial prescription.
- In addition, there is not only an important financial dependency of veterinarians on their clients, competition between veterinarians also comes also into play.
- Just like in other countries, for many Belgian veterinarians drug sales contribute to their income. Hence prescribing less, runs counter to their own interest. Research on this conflict of interest puts the importance of drug sales as a driver for antibiotic use into perspective, arguing that antibiotics are too cheap to be profitable.
- Several reasons have been cited for not following guidelines on the prudent use of antibiotics: easier administration, shorter withdrawal period for slaughter or milk delivery, treatment initiation in the case of critically ill animals, limited choice because of a limited number of authorized medicines for minor species (e.g. rabbits), previous experiences, price or other economic factors and previous treatment failure.

6 INTERVENTIONS TO PROMOTE THE PRUDENT USE OF ANTIBIOTICS

6.1 Interventions to promote the prudent use of antibiotics in the human sector

In 1998, a EU conference held in Copenhagen made antibiotic resistance an official EU issue for the first time, and produced the 'Copenhagen Recommendations'.⁴⁵ This was soon followed by an EU Council Recommendation in 2001 exhorting the member states to follow and enact the recommendations from the Copenhagen meeting.⁵²

In this chapter, we describe under section 6.1.1 the Belgian interventions that are or have been implemented to promote the prudent use of antibiotics, as well as interventions that have not yet been implemented in Belgium but are under discussion, and their respective evaluation when available. Section 6.1.2 describes the interventions that have been implemented elsewhere, if they have been evaluated.

The Belgian actors involved in promoting the prudent use of antibiotics, such as BAPCOC and RIZIV – INAMI, are described in section 3.4.2.

6.1.1 *Belgian interventions to promote the prudent use of antibiotics*

6.1.1.1 *Method*

Only a limited number of Belgian interventions targeting the prudent use of antibiotics have been the object of publication in peer reviewed journals. We opted for collecting data on Belgian interventions in the human sector by interviewing experts from BAPCOC and the FOD – SPF Health, Food Chain Safety and Environment experts, presidents of each BAPCOC working group, representatives from RIZIV – INAMI, research groups and medical professional associations. Ad-hoc literature search for peer reviewed articles and grey literature was performed to identify the potential evaluations of each of these interventions. A preliminary list of Belgian interventions and



evaluation studies has been submitted for review and completed by these stakeholders.

The interventions described below are either currently being implemented or have been implemented or are planned or subject of discussion, at national, regional or local level.

6.1.1.2 *Antimicrobial stewardship programs*

In Belgium, antimicrobial stewardship programs (ASP, see Box 24) have been introduced at national level in 2007. ASP have so far mostly focused on the acute hospital sector and are further described in section 6.1.1.3.

Box 24 – Concept of antimicrobial stewardship

Antimicrobial stewardship is defined by the European Commission (EC) as an organisational or healthcare system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness.³ Antimicrobial stewardship programmes (ASP) are coordinated programmes that implement interventions to ensure appropriate antimicrobial prescribing. Currently there is no clear consensus on which interventions an ASP should comprise as this depends on the institution, the region, and the patient population that is served.²⁷⁰ However the ECDC has summarized the main actions involved:²⁷¹

1. Leadership commitment: ensuring the necessary resources in terms of staff, technology and budget are available;
2. Appointing leaders that are responsible for the overall programme and for antibiotic use;
3. Hospital-based teams, which include infectious disease specialists, clinical pharmacists and microbiologists, providing support to prescribers;
4. Proactive auditing of antibiotic prescriptions with feedback to team members;

5. Training and education for medical, pharmacy, laboratory, nursing, and non-clinical staff, as well as patients and their families;
6. Using evidence-based antibiotic guidelines and policies;
7. Using restrictive measures for antibiotic prescriptions (e.g., pre-approval and post-authorization requirements for specific antibiotics);
8. Monitoring antibiotic resistance and use, and making this information available to prescribers.

It may also include empirical therapy according to guidelines, de-escalation of therapy, switch from intravenous to oral treatment, therapeutic drug monitoring, use of a list of restricted antibiotics, bedside consultation, rapid diagnostic tools etc.²⁷² Further details on this concept and the evaluation of its effectiveness in other countries can be found under chapter 6.1.2.

6.1.1.3 *Interventions in the hospital sector*

ANTIMICROBIAL MANAGEMENT TEAMS IN HOSPITALS

The 1998 'Copenhagen Recommendations' included a recommendation that every hospital should establish an antibiotic team that includes clinical microbiologists, infectious disease specialists and other relevant clinical specialties.^{45, 273, 274} Since the nineties, there has been a move in Belgian hospitals to establish multidisciplinary antibiotic management teams (AMT) to improve antibiotic prescribing and contain antibiotic resistance.⁷ Federal initiatives for developing AMT in hospitals have started in 2002 by a pilot project in 36 hospitals.^{275, 276}

After a positive evaluation, AMT have been expanded to the national level in July 2007, with a legal framework and funding established in Royal decrees since 2008, as described in Box 25.^{275, 277, 278} AMT are mandatory in all acute care hospitals and large (i.e. 150 beds or more) chronic care hospitals. In addition, BAPCOC provides scientific support by means of advanced training, standardised evaluation of progress reports and national surveillance of antibiotic use in hospitals.^{7, 24} Trained hospital antibiotic managers are given the responsibility to carry out the antimicrobial



stewardship programs in the hospital and the annual action plan that is defined by the AMT.

Box 25 – Antibiotic management teams (AMT) in Belgian hospitals

According to the law, a hospital AMT must be multidisciplinary and includes at least the following members: a president of the hospital antibiotic management; the hospital infection control physician; a clinical microbiologist; a physician specialist in infectious diseases and/or medical microbiology and a hospital pharmacist.^{278, 279} The delegate/president of the hospital antibiotic management should be a physician specialist in infectiology and/or medical microbiology or specialised in internal medicine, lung disease, paediatrics, intensive care or clinical biology, and follow the interuniversity course in antibiotic management.²⁷⁸

Officially, the AMT missions have been defined as follows:^{278, 279}

- To develop and update the hospital formulary for anti-infectious drugs;
- To develop recommendations and clinical practice guidelines on antibiotic therapy and prophylaxis;
- To train health care workers on diagnosis, microbiology, epidemiology and appropriate treatment of infectious diseases;
- To perform audits of medical practices, compliance to formulary and recommendations, with feed-back to prescribers;
- To develop surveillance of local antibiotic use and AMR;
- To write an annual report to BAPCOC.

In 2018, 101 acute care hospitals and 6 large chronic care hospitals received a total budget of € 4.4 million divided among them according to their number of beds. These funds are intended to hire a trained manager for their AMT, but hospitals have not been given specific targets to reach and are thus left to determine their own interventions.²⁷⁹ In an evaluation published in 2010 and conducted among 112 hospitals, AMT comprised a mean number of 10 members (range 2-28).²⁷⁹

In a number of hospitals, two levels of antibiotic management are described. An antibiotic management committee decides on hospital policies and an antibiotic team (equivalent to the antibiotic stewardship team in the Netherlands) is implementing activities.

The following five activities are classically promoted by AMT in Belgium, and their content and results of evaluations are described in the next sections:^{279, 280}

- Restricted list of antibiotics for prescription
- Promotion of rapid parenteral to oral switch therapy
- Automatic stop order for antibiotic treatment
- Promotion of de-escalation of therapy
- Post-Antibiotic Prescription Review

The interuniversity training that has been developed to train the 'delegates in charge of antibiotic use management', is described under section 6.1.1.3.

The paragraphs below describe the evaluations of the activity of the AMT as a whole, while the evaluation of specific activities are described under the corresponding sections (in section 6.1.1.3). The pilot phase was evaluated in 2005.²⁷⁶ At national level, two AMT evaluations were based on self-reporting (in 2007 and 2011) and covered process indicators,^{279, 280} and one evaluation covered outcome indicators.²⁴

1. The **evaluation of the 2002-03 pilot phase** reports that all 36 hospitals had undertaken a wide range of measures: review of formulary, implementation of new clinical guidelines, restricted access to selected antibiotics, improvement of antibiotic susceptibility testing methods, development of antibiotic use database and analysis of antibacterial susceptibility data.²⁷⁶ The financing scheme allowed the implementation of 175 antibiotic management interventions, with a mean of 5 interventions per hospital. Education of prescribers was based on multimodal communication, i.e. using an average of 3.6 different communication channels per hospital. The study concluded that hospitals that received a financial incentive had developed multimodal antibiotic policy interventions independently of the hospital size and teaching status.

2. **BAPCOC audits**, based on AMT activity reports, describe the proportion of hospitals that implemented antibiotic stewardship activities between 2007, which was the first year of the national extension of AMT support (Table 43). The 2007 survey was based on the activity reports of 112 of the 116 Belgian hospitals using a structured questionnaire.²⁷⁹ The 2011 survey involved 105 of the 109 hospitals and highlighted the progress in the proportion of hospitals implementing the stewardship activities (Table 43).²⁸⁰ Table 43 shows significantly higher implementation rates in terms of the so-called 'prospective audits' with immediate feedback to the prescriber in the case of inappropriate therapy (which are similar to post-antibiotic prescription review, see section 6.1.1.3), the promotion of de-escalation therapy (see section 6.1.1.3) and for the promotion of rapid parenteral to oral switch (see section 6.1.1.3). A progression was also observed in the proportion of AMT that defined their activities and goals for the upcoming year, from 83% in 2007 to 94% in 2011. It also pointed to the high level of interactions between AMT and infection control and pharmacy committee, and the lower involvement of senior hospital management. However, there are no financial data on the actual use of AMT funding within hospitals.²⁴
3. The most recent **ECDC Point Prevalence Survey** (see section 4.2.1.2) indicates a median of 0.12 AMT full time equivalent (FTE) per 100 hospital beds in 2017.¹⁴⁰
4. A **study conducted by Sciensano** (formerly WIV – ISP) intended to evaluate the impact of the AMT by assessing the association between the timing of the national support to AMT and outcome data at patient level: antibiotics administered and patient stays in 1999-2010 for two specific indications, antibiotic prophylaxis for major lower limb orthopaedic surgery and management of pneumonia.²⁴ Three quality indicators for antibiotic use in hospitals were selected and the analysis adjusted for confounding factors. Between 1999 and 2010, the indicator related to the compliance to guideline for surgical prophylaxis increased from 53% to 71%, the ratio of oral to parenteral treatment for pneumonia increased from 0.72 to 0.97, and the mean DDD of antibiotics (except penicillin) per 100 hospital days for pneumonia declined from 96 to 64. However, no positive effect could be statistically related to the timing of the AMT policy implementation at national level. The authors suggest

that the changes observed may also reflect multifactorial and continuous change processes of quality improvement in Belgian hospitals.

Table 43 – BAPCOC evaluation of the implementation of antibiotic stewardship initiatives (%) in the acute care hospitals, 2007-2011

	2007	2008	2009	2011
Number participating hospitals (% total)	112 (96%)			100 (97%)
Antibiotic formulary	96	96	96	97
Guidelines for antibiotic therapy	92	91	92	91
Guidelines for antibiotic prophylaxis	96	94	98	93
Antimicrobial order forms	36	43	42	47
Restricted list of antibiotics	76	76	81	79
Prospective audit with feedback	64	77	85	92
Automatic stop order	44	43	46	52
De-escalation therapy	64	91	93	93
Parental to oral switch	79	82	89	86
Analysis of antibiotic use	96	97	98	97
Analysis of antimicrobial resistance	90	94	95	96

Source: Van Gastel et al., 2010^{279, 280} and Van Gastel et al., 2015²⁸⁰



A few other published evaluations focused on the effect of AMT activities in specific Belgian hospitals.^{281, 282} In CHU Liège, a prospective study used interrupted times series analysis in the period 2012-14 to compare the quality of the documentation on antibiotic therapy in the medical records before and after the intervention.²⁸² The AMT intervention consisted of the implementation of guidelines, distribution of educational materials, educational outreach visits and group educational interactive sessions. A significant increase in the quality indicators was observed between the pre- and post-intervention period: indication documented 83% to 90%; antibiotics documented 88% to 96% and duration or review date documented 32% to 68%. In Ghent University Hospital, the AMT initiated a multidisciplinary infectious diseases team (MIT) to make recommendations on antibiotic therapy appropriateness and parental to oral switch (see section 6.1.1.3). Data from 2011-12 showed a high level of acceptance (83%) of the 432 MIT recommendations.²⁸¹ A number of other studies assessed the compliance of hospital physicians with specific AMT recommendations or guidelines for specific indications or specific patients, and are not further described here.²⁸³⁻²⁸⁵

RESTRICTED LISTS OF ANTIBIOTICS

The hospital formulary is a list of medicines that is legally mandatory for each hospital, which must be established on the basis of rational and economic criteria. These medicines must always be available in the hospital to respond to the diagnostic and therapeutic needs.²⁸⁶ The antibiotic part of the formulary is included in the AMT missions according to the royal decree 2008 and consists in a limited list of antibiotics that reflects the recommendations of the antibiotic policy, and that allows a normal clinical practice in the hospital.^{278, 287}

In addition, many hospitals have defined a second list of 'restricted antibiotics' that require justification for their use and either prior approval or post hoc review by the AMT for delivery by the hospital pharmacy.^{279, 287} In practice, these antibiotics can only be ordered by specific specialists, based upon specific microbiological results and/or clinical characteristics of the patient, in order to limit their use.²⁸⁰

BAPCOC audits of AMT revealed that most hospitals had developed an antibiotic formulary (Table 43), and above three quarters of hospitals reported to have defined a restricted list of antibiotics in 2007-11.^{279, 280} A BAPCOC evaluation was conducted in 2016 through questionnaires sent out to all hospitals, and included the criteria and antimicrobials concerned but the results were not published. (BAPCOC, *personal communication*) We did not identify an evaluation that measured the impact of this measure alone. A multi-country study evaluated the impact of MRSA policies, which included antibiotic restrictions in Belgium, by comparing the MRSA prevalence before and after the policy implementation in seven EU countries.²⁸⁸

PROMOTION OF RAPID PARENTERAL TO ORAL SWITCH THERAPY

Hospitalized patients initially on parenteral antibiotics can be switched to an oral equivalent within a few days of admission once clinical stability is established. The promotion of and guidance for the rapid switch from parenteral to oral therapy is part of the AMT activities.²⁸⁰ Specific criteria must be set to switch automatically patient on antibiotic treatment, and these can be communicated by poster, through the hospital intranet and spread to every hospital ward.²⁸⁹

BAPCOC studies have evaluated the proportion of hospitals that reported to promote this switch (Table 43).^{279, 280} Between 2007 and 2011, the proportion of Belgian hospitals reporting to switch as early as possible from parenteral to oral therapy increased from 79% to 86% hospitals, respectively, but no patient data were included.^{279, 280} Another national study based on medical files showed that the ratio of oral to parenteral treatment for pneumonia in hospitals increased from 0.72 to 0.97 between 1999 and 2010.²⁴ A study in the UZ Leuven hospital investigated the impact of direct phone contact between pharmacist and clinician on the intravenous to oral switch. Clinicians were contacted concerning 377 patients, but the switch was made for only 59% of patients. The study concluded that there are still some aberrant opinions circulating in the hospital environment regarding this strategy.²⁸⁹ However, no evaluation has measured the impact of this measure on the antibiotic use or patient morbidity or mortality.



PROMOTION OF DE-ESCALATION OF THERAPY

An 'appropriate antimicrobial therapy' requires that the causative pathogen is susceptible to the antibiotic regimen and that this regimen is initiated early at optimized doses.²⁹⁰ Due to the delays in obtaining microbiological results on the pathogen, physicians usually prescribe an empiric treatment, i.e. a regimen targeting the most likely pathogen based on the local epidemiology and the patient characteristics. The de-escalation of therapy is defined as the change of an empirical therapy to a narrow-spectrum antibiotic on the basis of susceptibility of the identified pathogen(s), or to the stop of antibiotic therapy after a few days, on the basis of clinical evolution and microbiological results.^{272, 279, 290} This is also called streamlining of empirical therapy, and aims at limiting prolonged patient exposure to broad-spectrum antibiotics.

In Belgium, this strategy is actively promoted for certain indications (e.g. sepsis) or for patients in certain units (e.g. intensive care units). BAPCOC audits showed that the proportion of hospitals that reported promoting de-escalation of therapy after a few days increased from 64% in 2007 to 93% in 2011 (Table 43).²⁸⁰ No outcome evaluation of this measure in Belgium was found, except for one study in the Ghent University Hospital, which assessed the impact of the de-escalation of beta-lactam antibiotics against pseudomonas in intensive care units.²⁹¹ The duration of the antibiotic course was longer de-escalated (8 days) versus continued prescriptions (5 days), mortality did not differ between the two groups and data on emergence of resistance to the initial beta-lactam antibiotic suggested that de-escalation was not associated with a lower emergence of antibiotic-resistant bacteria.²⁹¹

AUTOMATIC STOP ORDER FOR ANTIBIOTIC TREATMENT

Automatic stop order refers to the systematic stop of the delivery of an antibiotic by the pharmacy after a defined number of days (e.g. 3 days) and the re-evaluation of medical and microbiological information to request extension. This strategy is promoted by AMT in Belgium.²⁷⁹ For instance in Cliniques universitaires Saint-Luc in Brussels since 2007-08, an automatic stop occurs at day 3 for intravenous therapy and at day 5 for oral antibiotics. Continuation of therapy requires a simple click on the hospital IT programme. Another option is a message sent to propose to revise the therapy after unnumber of hours.²⁹²

However, according to BAPCOC audits of AMT, only 44% and 52% of Belgian hospitals reported to use this measure in 2007 and 2011, respectively (Table 43).^{279, 280} There is indeed some level of reluctance in some hospitals to install such system because of the fear that physicians will not renew the prescription in time, especially during the weekend. No outcome evaluation of this measure in Belgium was found, but non-published audits from Cliniques universitaires Saint-Luc in Brussels estimated that the system resulted in a 2-days reduction in the mean duration of piperacilline & tazobactam (Tazocin®) treatment between 2003 and 2010.²⁹²

POST-ANTIBIOTIC PRESCRIPTION REVIEW

Post-antibiotic prescription review (PAR) refers to a measure in which antibiotic prescriptions for certain indications or certain patients on certain units, or for certain antibiotics, are checked daily by a member of the AMT and then discussed with the bed-side physician in the case of inappropriate therapy. PAR can be solicited or be automatic. BAPCOC calls this strategy 'prospective audit with feedback', which may be confused with hospital audits. Belgian hospital AMT may define different PAR strategies. Some hospitals keep a list of patients receiving antibiotics that need to be regularly reviewed. In Ghent University Hospital, PAR is conducted by a multidisciplinary infectious disease team (MIT) comprising an infectiologist, a clinical microbiologist and a hospital pharmacist. MIT focuses on patients with positive blood cultures, multi resistant strains, patients on carbapenems, or patients under long antibiotic treatment.²⁸¹ The MIT issues a motivated advice which is communicated immediately by phone and entered in the electronic patient file.

At national level, BAPCOC audits indicate that the proportion of hospital AMT conducting daily PAR increased from 64% in 2007 to 92% in 2011.²⁸⁰ An evaluation of the MIT in Ghent University Hospital showed that around 80% of their PAR recommendations are accepted by the prescriber.²⁸¹ No outcome evaluation of this measure in Belgium has been found. However, the 2017 ECDC PPS (described in section 4.2.1.2) conducted in 43 Belgian hospitals revealed that only 18 of the 41 responding hospitals had a formal procedure for post-antibiotic prescription review in the hospital.³⁹



POLICY FOR MRSA MANAGEMENT IN ACUTE CARE HOSPITALS

In 1993, a Belgian policy was introduced for the management of Methicillin-resistant *Staphylococcus aureus* (MRSA) in acute care hospitals. The policy included guidelines for the management of MRSA in nursing homes (2005) and the revision of guidelines for acute care hospitals (2003), microbiological and epidemiological surveillance, and the improvement of identification techniques for MRSA in hospital microbiology laboratories.²⁹³ The policy also covered guidelines for prophylaxis and restriction of antibiotics.

A Belgian study conducted by Sciensano reported changes in resistance rates (MRSA/ *S. aureus*) in acute care hospitals, which declined in the period 1994-1998, from 24% to 14%, then increased to 31% in 2003 and declined again up to 21% in 2010.²⁹³ These changes reflect the results of bundled actions of MRSA policy. A multi-country evaluation of MRSA policies compared the MRSA prevalence before and after the policy implementation in seven EU countries (1999-2015).²⁸⁸ MRSA prevalence in Belgium declined by 44%, from 22% in 1999 to 12.3% in 2015. The decline was more substantial in countries with more extended MRSA policies (including Belgium) than in countries with few policies.²⁸⁸

INTERUNIVERSITY TRAINING IN ANTIBIOTIC MANAGEMENT

An interuniversity course in antibiotic management is offered to train the hospital 'delegates in charge of antibiotic use management'. It is partly funded by BAPCOC, and the minimal requirements are defined in the 2008 RD (Annexe A).²⁷⁸ These courses are organised every two years in both sides of the country, and a national study day is taking place on the alternate year to support the AMT.⁷⁷

- On the French speaking side, a course leading to a certificate in antibiotic management ('Certificat en gestion de l'antibiothérapie') is jointly organised since 2002 by an interuniversity consortium of the Université catholique de Louvain (UCL), the Université libre de Bruxelles (ULB) and the Université de Liège (ULg), BAPCOP and the

FOD VVVL – SPF SPSCAE, from October to May.^{vv} The 2018-19 programme has a duration of 50 hours in one academic year, spread in 10 days.

- On the Dutch-speaking side, the Catholic University of Leuven (KU Leuven) is organising with Ghent University, the Free University of Brussels and the Antwerp University a course of 31 hours (6 days) on antibiotic policy ('Interuniversitaire opleiding in antibioticabeleid').^{ww} Around 80 professionals (medical specialists and pharmacists, including specialists in clinical biology) are trained every two years.

AUDIT AND FEEDBACK TO HOSPITAL PRESCRIBERS ON ANTIBIOTIC USE

Audit and feedback is widely used as a strategy to improve professional practice and is based on the belief that healthcare professionals are willing to modify their practices when they receive performance feedback showing that their clinical practice is inconsistent with a desirable target.²⁹⁴ In Belgium, there are many initiatives, at national or hospital level, that analyse antibiotic use data and provide feedback on prescription patterns to the hospital prescribers. This type of feedback should be distinguished with post-antibiotic prescription review (PAR, described above) in which the management of specific patients are discussed with the treating physician.

At hospital level audit and feedback is done by the AMT. Indeed, one of its missions is to develop and manage a system that monitors local antibiotic use profiles in the hospital, per ward and per prescriber, and to regularly inform the prescribers and the hospital management on the amounts and costs of anti-infectious treatments.²⁷⁸ The BAPCOC audit indicated that the majority of hospitals are conducting these activities (Table 43). In the 2007 audit, 88% of hospitals that analysed antibiotic use data provided feedback to the prescribers, but only 20% of these hospitals analysed data for each ward.²⁷⁹ This was not documented in the 2011 audit.²⁸⁰ No outcome evaluation of this measure in Belgium has been found.

^{vv} http://www.hospitals.be/images_produit/upload_fichier/423_Annonce-cours-GA-2018-2019-aff.pdf

^{ww} <http://www.bvikm.org/media/docs/NAC/Bijzondere%20Opleiding%20Antibioticabeleid/Programma%20BOA.pdf>



At national level, a number of projects are (or were) monitoring hospital antibiotic use (see also section 4.2.1.1). Only the feedback aspects are developed in this section.

- A compulsory national surveillance is conducted by Sciensano. The ABUH project collected antibiotic use data from hospitals in the period 2007-2013. The interface provided immediate access to hospital antibiotic use trends as well as benchmarking indicators, as soon as data were entered in the application. However, no data on patient age or diagnosis were registered, nor any information related to the prescriber. In 2012, the participation to ABUH was estimated at 88%.¹¹⁶ The BeH-SAC projects took over this monitoring in 2013 and data are extracted from RIZIV – INAMI. Feedback can be accessed through the Healthstat platform and includes benchmarking as well. Analyses contain more variables but are not presented per ward or per prescriber (see also section 4.2.1.1).¹¹⁷
- Two Point Prevalence Surveys (PPS) cover the use of antibiotics in hospitals and aim to provide feedback to hospitals. The prevalence survey records the antibiotics used in a single ward on a single day; participation is not mandatory also (see also section 4.2.1.2).
 - The ECDC coordinated two PPS, organised in Belgium through Sciensano, which collect data at hospital, ward and patient level.²⁹⁵ ECDC is generating individual feedback reports (in English) for each participating hospital, as a standardised tool to identify targets for quality improvement. In 2017, 43 Belgian hospitals participated to the ECDC PPS.³⁹ Results of the ECDC PPS have been published (see section 1.1.1.1) but no report on the feedbacks and their impact in Belgium was found.
 - Two 'Global PPS' have been conducted in Belgium in 2015 and 2017. The system allows each participating hospital to download a feedback after data-entry. This takes the form of slides containing feedback on several antibiotic quality indicators (i.e. oral versus parenteral administration, guideline compliance) and hospital specific antimicrobial prevalence figures, plotted against overall mean national and regional results. In addition, hospitals can extract their own raw data in an Excel file, which can then be

analysed for own purposes.¹²³ These can be used for e.g. local communication. In 2015, 24% and 68% of primary and secondary hospitals, respectively, participated in the Global PPS.²⁹⁶ Results of the Global PPS have been published but no evaluation of the impact of the feedback reports in Belgium was found.

- Two audits on surgical antibiotic prophylaxis have been conducted and funded by the BAPCOC coordination in 2013 and 2017, using ECDC indicators. The 2013 audit was conducted by hospital AMT in 3 273 medical files from 77 acute care hospitals, based on a BAPCOC protocol and using a questionnaire.²⁹⁷ After each audit, hospitals received individual data on prophylaxis in relation to guidelines and compared to a national average. The 2017 audit was web-based and involved the sampling of 25 patient files per hospital for two selected interventions. All hospitals received their own individual result as well as overall results (2 reports in PDF, BAPCOC, *personal communication*). No outcome evaluation of this intervention in Belgium was found.

FINANCIAL INCENTIVES IN THE HOSPITAL SECTOR

A number of financial mechanisms for Belgian hospitals may favour the prudent use of antibiotics (see also section 3.3.1). The results of evaluations are reported below.

Surgery prophylaxis

Between May 1997 and July 2006, a fixed lump sum for antibiotic prophylaxis by surgical procedure was implemented, limiting the reimbursement of antibiotic prophylaxis to specific agents and a 24-hour period after surgery according to guidelines (see also section 3.3.1).

Three studies describe the impact of this measure by comparing data before and after the introduction.^{67, 298, 299} Between 1986 (pre-intervention) and 1999 (post-intervention), the proportion of appropriate perioperative antibiotic prophylaxis improved, with an increase in the proportion of patients with correct timing (from 53% to 70%) and a reduction from 50% to 8% of patients with duration above 48 hours after surgery.^{66, 299} Analyses of expenses for antibiotics in patients admitted for surgery show a sharp decline after implementation of the measure.⁶⁷ Another analysis showed significant decreases in the proportion of patients with administration of



antibiotic prophylaxis of long duration (from 26% in 1992-96 to 19% in 1999-99, $p=0.014$) and those who received more than one antibiotic (17% vs. 7%, $p<0.001$).²⁹⁸ These results suggest a more rational use of antibiotic prophylaxis after the financial measure.

An EU study in 28 EU countries compared, in each country, the national uncertainty avoidance score (see section 5.1.1) to the national proportion of perioperative surgical prophylaxis beyond 24 hours among all surgical operations surveyed, based on data from the 2011-12 ECDC PPS (see section 4.2.1.2).¹⁵⁹ The author noted that Belgium was the only country to show a different association between these two variables, with a high uncertainty avoidance score (UA, based on Hofstede uncertainty avoidance score) and a low proportion of surgical prophylaxis beyond 24 hours (35%) compared to other countries, being thus an outlier in the regression model. He related to the changes in compliance to the criteria above described between 1986 and 1999 to the financial measure, and stated that such a top-down intervention is highly compatible with culture change in countries with high uncertainty avoidance. He also hypothesized that the uncertainty of financial losses from lack of reimbursement would have immediately become the most important element in the decision-making process and would have overcome the dogma of unnecessarily prolonging the prophylaxis.¹⁵⁹

Financing mechanism for hospital drugs

A new financing mechanism for all drugs used in hospitals took effect on July 2006 and introduced a fixed lump sum per group of disease to cover the cost of most medicines administered during inpatient stays (based on the hospital case-mix, a national average per APR-DRG and the severity of illness, see section 3.3.1).⁷⁰ One of the objectives was to provide an incentive for a more rational use of drugs in hospitals.

A Sciensano study, aiming to assess the impact of this measure, reported that antibiotic use for patients admitted to Belgian hospitals for pneumonia and major lower limb orthopaedic surgery without trauma improved steadily between 1999 and 2010, based on indicators of compliance with clinical guidelines. However, the statistical modelling exercise did not detect an association with the year of introduction of the new system (2006) in two selected quality indicators for pneumonia antibiotic treatment. The authors

concluded that the improvements observed could not be related at the national level to the policy being studied, and may be due to multifactorial and continuous change process of quality improvement.^{24, 300}

Pay-for-Performance

Pay-for-performance (P4P), also called by some 'pay-for-quality', is a funding mechanism that proposes to directly relate the remuneration of delivered care to the achieved results on structure, process and/or outcome indicators.³⁰¹ In Belgium, a national P4P programme was launched on 1 January 2018 for general hospitals.³⁰² A set of P4P indicators for funding of general hospitals has been defined in 2018 and includes three (process) indicators related to antibiotic prophylaxis for three specific surgical interventions. A compliance of 90% is the target to obtain the maximum score for that indicator. In addition, the participation to three non-mandatory audits favouring the quality in terms of antibiotic use, the ECDC PPS, the Global PPS and the BAPCOC audits on antibiotic surgical prophylaxis, are considered as P4P indicators in this system. As this mechanism is recently introduced, no evaluation has been yet identified.

QUALITY ASSURANCE AND HOSPITAL ACCREDITATION

In Belgium, hospitals have to satisfy a set of quality standards which are monitored by the communities. In Flanders, the Flemish Agency for Care and Health is running the Vlaams Indicatorenproject voor Patiënten en Professionals (VIP²), which measures the quality of care in most Flemish hospitals. The hospitals select the indicators they want to measure, and the results are published on www.zorgkwaliteit.be if they opt for it. However, no indicator related to antibiotics is currently listed (as of January 2019). In Wallonia, the plan 'quality of health care' does not propose a specific monitoring but promotes that hospitals seek accreditation.

Many Belgian hospitals indeed seek an external quality accreditation by independent agencies, on a voluntary basis. Accreditation is defined as 'initiatives to externally assess hospital against pre-defined explicit published standards in order to encourage continuous improvement of the health care quality'. The two accreditation systems that are used in Belgium include quality indicators related to prudent use of antibiotics. The Nederlands Instituut voor Accreditatie in de Zorg (NIAZ) runs the NIAZ-Qmentum



accreditation programme, which recently included antibiotic stewardship as an indicator (e.g. the hospital has guidelines for the prescription and administration of antibiotics). The Joint Commission International (JCI) has accreditation standards for hospitals that addresses issue related to antimicrobial resistance, such as the requirement for the antibiotic stewardship programme to involve infection prevention and control professionals as well as physicians, nurses, pharmacists, trainees, patients, and families, and the need for proper use of antibiotics for prophylaxis and treatment. No impact of these accreditation systems has been found.

6.1.1.4 Interventions in nursing homes

INTRODUCTION

Every Belgian nursing home (NH) has to meet accreditation standards which guarantee basic quality in care. The recognition of a nursing home is granted by the Communities/Regions; their inspection services monitor compliance to these standards. But also RIZIV – INAMI supervises certain aspects of care; it concerns (among others) the correct prescription and administration of medicines and the under- or overuse of medicines.³⁰³

The vast majority of residential care centres are also recognized as 'Rest and nursing home' ('rust- en verzorgingstehuis (RVT)' – 'maison de repos et de soins (MRS)'). This means that places ('RVT beds' – 'lits MRS') are available for the care of severely dependent elderly.³⁰⁴ The national health insurance (RIZIV – INAMI) contributes to part of the care^{xx} of the residents of nursing homes through lump sums; the amount of the RZIV – INAMI contribution depends on the residents' care dependency as well as on the care staff's qualifications and seniority.³⁰³

ANTIBIOTIC STEWARDSHIP IN NURSING HOMES

One of the recognition criteria of a nursing home is the appointment of a 'coordinating and advising physician' ('coördinerend raadgevend arts (CRA)'

– 'médecin coordinateur et conseiller (MCC)'), who should be a GP who followed a dedicated training (certificate).³⁰⁵ This training includes a topic on 'the prevention of infections and the management of antibiotherapy', but the role in antibiotic stewardship is not described. The CRA – MCC should supervise drug stewardship in general, such as the organization of drug prescription and delivery, as well as the establishment of a drug formulary, and this encompasses antibiotics. In addition, the CRA – MCC should manage healthcare associated infections.

In real terms, the input and impact of the coordinating and advising physician varies considerably among NHs. (Vlaams Agentschap Zorg en Gezondheid, *personal communication*) This is closely related to the fact that every NH resident can choose his own GP, leading to many GPs taking care of the residents of a nursing home.³⁰⁶ This may result in an inconsistent approach to the diagnosis and management of infections, with an overuse of antibiotics and a tendency to overuse broad-spectrum antibiotics in particular. Even more, the coordinating physician does not have access to other clinicians' patient files and prescription records because of privacy rules.⁷⁶ The coordinating physician does not have any real possibility to train other GPs or to harmonise their diagnostic and prescription practices. This situation makes a coherent policy e.g. with regard to the prudent prescription of antibiotics not straightforward.

In the national plan for MultiDrug-Resistant Organisms (MDRO, 2013) some antibiotic stewardship activities in the NH are proposed (see section 6.1.1.6), such as the setup of an antibiotic formulary and antibiotic guidance, and a number of antibiotic guidelines have been issued (see section 6.1.1.8).³⁰⁷ The feasibility of this proposal was evaluated in 2010-11 by a pilot project in four NH consortia (groups of NH and one reference hospital), and the pilot was extended to two other consortia in 2014. Two evaluations have been published in 2017 and 2018.^{308, 309} One consortium in Ghent published its experience but only includes the experience of one CRA – MCC in terms of policy of restrictive use of antibiotics.³⁰⁹ A report of the entire pilot experience has been published in 2018 by the FOD VVVL – SPF SPSCAE but it rather

^{xx} The care paid by the national health insurance (RIZIV – INAMI) includes: help with day-to-day activities, personal hygiene, nursing care, tasks of

(re)activation, rehabilitation and social (re)integration. RIZIV – INAMI calculates for each nursing home a lump sum; the resident's health insurance pays that lump sum to the nursing home.



contains a set of evidence- and expert-based recommendations and no an evaluation of the antibiotic policy aspect.³⁰⁸ However, a few findings are reported. General practitioners have difficulties to find time for continuous training, which also represents a loss of profit as they are not paid for that time. The diagnostic uncertainty was a frequent cause of inappropriate antibiotic prescribing, and diagnostic aids should be made available. Antibiotic treatments for asymptomatic bacteriuria and colonised wounds represent particular problems of over-prescription.³⁰⁸

An evaluation of the role of the CRA – MCC in antibiotic stewardship activities in NH has been conducted in 2014, based on interviews.³¹⁰ Questionnaires were completed by 39 CRA – MCC from the three regions of Belgium, i.e. 12% of the contacted CRA – MCC. Past or present implementation of an antibiotic stewardship programme was reported in 23% of NH. CRA – MCC felt often helpless, as not sufficiently empowered to correct their colleagues. The lack of antibiotic guidelines in the NH was reported by 29% of respondents, and when they were available, they were underused (see further details under section 6.1.1.8).

FEEDBACK FROM POINT PREVALENCE SURVEY IN NURSING HOMES

Since 2009, three point prevalence surveys (PPS, see section 4.2.1.2) of healthcare-associated infections and antimicrobial use in European long-term care facilities (LTCF) have been organised and funded by ECDC (HALT, see section 4.2.1.2).³¹¹ The 2017 report published the results of the 2016 HALT survey, which involves data from 165 Belgian LTCF, including 158 NH.³¹² The prevalence of residents with at least one antimicrobial was 5.5 % (95%CI 0-18%), compared to 4.6% and 5.1% in 2010 and 2013 HALT surveys, respectively. Only 19% of institutions had a monitoring system for antibiotic use. The report did not issue recommendations. However no information on the type of feedback that has been provided to nursing homes on these results and on the impact of this feedback has been found.

PRESCRIPTION BY UNIT

Within the frame of an austerity measure issued in 2015, aiming at a reduction of the volume of medicines delivered to elderly, systemic solid medicines (e.g. tablets) reimbursed by the health insurance, such as antibiotics, are no longer dispensed and billed per package but per unit and

per 7-day period.³¹³ The pricing is based on the unit prices (reimbursement basis and per unit contribution) which are published monthly by RIZIV – INAMI. The price is determined on the basis of the largest available public package which is reimbursed. The pharmacist receives a weekly fee (anno 2018 €3.25 incl. VAT) per nursing home resident to whom he delivers medicines. No evaluation of this measure has been identified.

6.1.1.5 Interventions in the ambulatory sector

There is no organised or funded antibiotic stewardship initiative at ambulatory level, as opposed to the hospital sector.

CAMPAIGNS PROMOTING THE RATIONAL USE OF ANTIBIOTICS AMONG AMBULATORY PRESCRIBERS

Since 1999, national campaigns are organised every year for the prescribers of the ambulatory sector (GPs, paediatricians, pneumologists, ear nose and throat specialists and community pharmacists), together with a mass campaign targeting the general public. Prescribers receive personal letters together with the campaign material for patients.³¹⁴ The content of the message is adapted every three years.

A number of studies have evaluated the impact of different national campaigns on clinician perception, public awareness and antibiotic use.^{163, 164, 171, 314-317} We only report here the results on GP perception. Changes in antibiotic use and in public perception are described under the national campaigns (see section 6.1.1.7), as identifying the separate impact of each component of the campaign is difficult.³¹⁶

A first study assessed the impact of the first two campaigns through pre- and post-campaign telephone interviews of around 400 GPs in 2001 and 2002.^{314, 316} The first campaign had a high visibility (100% GPs) and 63% GPs shifted opinion in favour of using antibiotics more sparingly. However one-third of GPs perceived the campaigns as a mean to reduce social security costs.³¹⁴ The second campaign had a lower visibility (73%).³¹⁶

Three qualitative studies among French speaking GPs have assessed in 2006-10 the reasons why the campaigns lacked effectiveness, through focus groups, a Lot Quality Assurance Group study and a large survey using a self-administered questionnaire.^{163, 164, 171} The reasons for prescribing an



antibiotic against the guidelines and against the messages of the public campaigns were medical, socio-cultural and related to guidelines, and are further described in section 5.1.1. The authors suggest that the campaigns lacked effectiveness because they have missed the real target, i.e. the sick patient and the attending physician, and did not address the real question of importance for those two actors, such as diagnostic uncertainty for the physician (i.e. what is the diagnosis, what are the risk of not giving an antibiotic, and will the patient go and see another doctor?) and for the patient (am I going to take a risk for myself and what for my child or my parent?).¹⁶⁴ However, GP considered public campaigns as justified because they tend to decrease patient's demand.^{163, 171}

FEEDBACK TO PRESCRIBERS ON ANTIBIOTIC PRESCRIPTION PATTERNS

Improving the quality of medical practice classically involves the feedbacks on prescription data to individual physicians to help them gain knowledge. In Belgium, national feedback campaigns have been launched in the 90ies for ambulatory care prescribers, and the first priority was to optimise the prescription behaviour of antibiotics.

Farmanet – Pharmanet, created in 1996, contains data on GP prescriptions for all pharmaceutical products reimbursed by the compulsory health insurance and delivered by the pharmacies open to the public (see section 4.2.1.1 for further details). One of the objectives of Farmanet – Pharmanet is to promote a more rational use of antibiotics by providing feedback to prescribers on their prescription behaviour and compare it to the one of their peers (e.g. doctors of a particular specialty).³¹⁸

In practice since 1998, periodic feedbacks have been sent to each GP or grouped practices on her/his individual prescription profile, before the creation of BAPCOC and antibiotic information campaigns, and in some years to other medical specialists prescribing antibiotics in ambulatory

care.³¹⁸ The feedback data are meant to be discussed in local quality circles (cf. infra). In 2000, the RIZIV – INAMI 'information cell' was created to integrate these prescription data together with the recommendations, with the mandate to organise a sensitisation programme for the rational prescription of specific medicines and to spread it through the local quality circles ('Lokale Kwaliteitsgroep' – 'Groupe Local d'Évaluation Médicale', LOK – GLEM).³¹⁹ In 2002, the information cell, together with the Platform for Quality Promotion,^{yy} organised the first antibiotic feedback. In late 2002, the RIZIV – INAMI National Council for Quality Promotion (NCQP, see section 3.4.2), including GP representatives, has been created to define the content of the feedback reports for prescribers and to supervise the campaigns.³¹⁹ The objectives are to inform GPs on antibiotic recommendations, provide a view on how they prescribe antibiotics and to promote the prudent use of antibiotics.³¹⁹ The scientific associations of GPs (Société Scientifique de Médecine Générale (SSMG) – Domus Medica) also organised training sessions for LOK – GLEM moderators to ensure that a robust and standardised message would be provided when discussing the feedback reports in the LOKs – GLEMs. Since 2003, the NCQP has periodically sent feed-back reports on antibiotic prescription to GPs and grouped practices.

Feedback reports comprise the individual GP prescription profile, comparison with the average and the colleagues from the same LOK – GLEM, using the BAPCOC guidelines as reference for practice.^{zz} All GPs that have more than 200 patients and prescribed more than 10 antibiotic treatments in a given year receive individual feed-back. Data are standardised to account for the number of patients seen and the number of patients on the GP list. Feedback on the prescription covering 2001, 2003, 2006 and 2007 have been sent.³²⁰ Ambulatory specialists, i.e. paediatricians, ear-nose-throat specialists, lung specialists and urologists active in ambulatory care received 2002 data in 2004. In addition, RIZIV – INAMI sends regular feedback on the proportions of antibiotics prescribed by antibiotic class to each LOK – GLEM together with data on other

^{yy} Includes members of INAMI, Intermutualistic agency (IMA – AIM), KCE, scientific associations of GPs (Société Scientifique de Médecine Générale (SSMG) – Domus Medica), ABSYM, CARTEL, and works under the RIZIV – INAMI National Council for Quality Promotion

^{zz} <https://www.inami.fgov.be/fr/themes/qualite-soins/medicaments/Pages/feedback-prescription-antibiotiques.aspx>



prescription topics.^{aaa} Data on antibiotics prescribed in 2013 have been sent in 2015. GPs also received from RIZIV – INAMI a few indicators on antibiotic prescription included in their 2011 ‘Personal activity report’.^{bbb} The most recent ‘Personal activity report’ was sent to GPs in February 2019.^{ccc} The 2-3 year delay is due to the time needed to receive all reimbursement data (as reimbursement is possible up to 2 years after the consultation) and to match prescription data to the number of patients seen and the number of patients on the GP list.

Three older KCE reports have assessed the effectiveness of prescription feedbacks in the literature,^{319, 321, 322} and one published in 2006 has assessed it among Belgian GPs.³²² That study evaluated the acceptance and influence of the antibiotic feedback on GP perception and practice, by organising 10 focus group discussions with GPs (five per language) and 2 focus group discussions with LOK – GLEM moderators in 2005.³²² The study revealed that the majority of GPs felt uncertain regarding the feedback objectives, because they distrust RIZIV – INAMI (as being in charge of controlling – and thus reducing expenses) and perceived that they conceived the feedbacks. Authors reported a change in their prescription behaviour following the feedback and LOK – GLEM discussions, but this concerned more the choice of the antibiotic prescribed than the fact to prescribe or not. This change has not been sustained over time, and a number of GPs felt that the feedback had no or limited impact. Some GPs did not agree with or were reluctant to the clinical recommendations that were provided together with feedbacks. They felt these recommendations missed to take the constraints of daily practice into account and they did not perceive them as based on evidence. A majority of them also considered the content of the feedback as too complex, especially the statistical part, and too long. They were disappointed that the data did not take into account contextual aspects of the practice (e.g. social and morbidity characteristics, organisation) and questioned the relevance of the mean as reference. Some GPs regretted the long delay between the prescription and reception of the feedbacks, as these did not represent the practice at the time of receiving feedbacks. GPs

consider that the feedback discussion in LOK – GLEM was necessary to stimulate GPs to read and understand feedbacks and to interpret and discuss data (cf. *infra*). The study concluded that feedbacks are mostly targeted at knowledge and attitude, and therefore only target some of the determinants of the prescribing behaviour. Authors conclude that the feedback document and the discussion with the LOK – GLEM are interdependent and complementary interventions. Feedbacks are part of a long and complex process of change.³²²

Another evaluation of the impact of the antibiotic feedback together with financial measures targeting GP on quinolone prescription and resistance is described below.³¹⁸

In its 2014-19 plan, BAPCOC indicated that ‘the feedback of antibiotic use and outpatient antibiotic resistance data to GPs should also be improved’.⁷⁷

E-LEARNING AND EDUCATION MATERIAL FOR GENERAL PRACTITIONERS

Besides clinical guidelines, a number of educational materials on the prudent use of antibiotics have been developed for GPs in Belgium.

The European GRACE INTRO project (Genomics to combat Resistance against Antibiotics for Community acquired lower respiratory tract infection in Europe – INternet TRaining for antibiOTic use) developed internet-based training tools for lower-respiratory-tract infections in Europe, mostly focused on communication skills. The internet-based learning package of GRACE INTRO corresponds to one-hour training, has been first tested in a randomized trial in 2011 and evaluated at European level.³²³ Antwerp University was partner in that EU project and the GRACE INTRO training has been tested in Antwerp practices in the European level evaluation (as part of a cluster randomised trial, see below).³²³ Since 2017, GRACE INTRO is implemented at national level, in collaboration with RIZIV – INAMI and the FOD VVVL – SPF SPSCAE, as part of the e-learning and continuous

^{aaa} <https://www.inami.fgov.be/fr/professionnels/sante/medecins/qualite/feedback/Pages/glem-feedback.aspx>

^{bbb} <https://www.inami.fgov.be/SiteCollectionDocuments/generalistes-rapport-activite-2011-exemple-feedback.pdf>

^{ccc} https://www.riziv.fgov.be/nl/professionals/individuelezorgverleners/artsen/kwaliteit/feedback/Paginas/verslag-activiteit-huisarts-2016.aspx?utm_source=alert&utm_medium=email&utm_campaign=NL2019_0207



education activities (CME). An invitation was sent to all Belgian GPs together with patient information booklets to be used interactively during the consultation. The e-training is available on the e-learning part of the FOD VVVL – SPF SPSCAE website (on <https://www.health.belgium.be/en/node/29004>).

A short 10-minute version of this training, TRACE (Translational Research on Antimicrobial resistance and Community-acquired infections in Europe), has also been made available on the same e-learning platform, and is accompanied by a booklet. TRACE has been progressively deployed among Belgian GPs in 2017-18, by province.

The European evaluation of GRACE INTRO perception and effectiveness is described under the sections on enhanced communication skills and point-of-care testing (cf. infra). The Belgian implementation of GRACE INTRO and TRACE has not yet been evaluated, but this is planned.⁷⁷

A few others information or educational materials have been identified. A newsletter, Medflash, which include some topics on antibiotics, has been distributed by the Platform for Quality Promotion to all primary care physicians in 2004, 2005 and 2006.³²⁰ It contained data on prescriber use of medicines, with a section on antibiotics prescription. Articles on the rational use of antibiotics in ambulatory care are published in October of each year in the Folia Pharmaceutica. It generally addresses the treatment of acute respiratory or urinary tract infections, contain update on literature, data on AMR, BAPCOC work and clinical recommendations.^{ddd} A 2016 RIZIV – INAMI newsletter (Infospot) described 2014 data on antibiotic use among children in ambulatory practices. No evaluation of these materials was found.

QUALITY CIRCLES AND SMALL GROUP EDUCATIONAL MEETING

In Belgium, the main quality circles are the so-called 'local groups for medical evaluation' (LOK – GLEM). These are defined by RIZIV – INAMI as a group of peers, physicians or pharmacists biologists, who share and evaluate critically their own medical practices (peer review) to promote health care quality. Physicians must participate to a LOK – GLEM to obtain or maintain

their accreditation. Additionally in the French speaking part, other groups of peers, the Dodécagroupes, are small groups of GPs who meet around 10 times annually to discuss a topic related to their current practice, together with an external expert.^{eee}

One of the objectives of LOK – GLEM is to discuss the results of the individual feedback reports and therefore enhance their impact on daily practice.³²¹ The RIZIV – INAMI feedbacks on antibiotic prescriptions were meant to be discussed in the LOKs – GLEMs (see above). However, LOKs – GLEMs are free to decide whether they want to discuss prudent antibiotic use or not, and if so, whether this would include discussion on feed-back data. LOKs – GLEMs have no mandate nor mandatory activity regarding prudent antibiotic use, and no financial incentives to do so. Since 2011, up to four LOK – GLEM meetings a year are funded by RIZIV – INAMI (200€/meeting). One exception was a temporary increase in the fee-for-services of GPs conditional to the rational use of antibiotics which has been implemented in 2004-05 (cf. infra).³¹⁹ One condition was that each LOK – GLEM would organise at least one full session on the analysis and discussion of the feed-back provided by the RIZIV – INAMI.³¹⁹ As said above, GPs could be trained as LOK – GLEM moderators by the scientific associations of GPs on prudent antibiotic use and receive fees for the assistance to training sessions and for LOK – GLEM moderation.

Three KCE studies have evaluated the effectiveness of the LOK – GLEM meetings.^{319, 321, 322} One study evaluated the effectiveness of the LOK – GLEM discussion on antibiotic feedback by conducting focus group discussions in 2005 (see method under 'Feedback to prescribers on antibiotic prescription patterns').³²² The overall opinion of the GPs was more in favour of the LOK – GLEM discussion than of the feedback tool itself. The importance of the LOK – GLEM moderator was highlighted: the majority of participants considered that a trained LOK – GLEM moderator is necessary to understand the document, and otherwise LOK – GLEM meetings can be counter-productive regarding prudent use of antibiotics. The meeting was useful in stimulating GPs to read the document, allowing them to understand the content, discussing and interpreting the findings with peers. However LOKs – GLEMs did not often discuss the antibiotic feedback sent to

^{ddd} <http://www.cbip.be/fr/foalias>

^{eee} <https://www.ssmg.be/types-de-formations/>



individual GPs. The study concluded that the training of moderators is essential and that the content of LOK – GLEM meetings must be standardised, while keeping a level of flexibility according to the specificity of each LOK – GLEM.³²²

The effectiveness of a single intervention in LOKs – GLEMs for the implementation of a guideline for rhinosinusitis was assessed in 2004-05, through a cluster randomized trial conducted in primary care in Flanders.³²⁴ The LOK – GLEM session introduced and discuss a clinical guideline on the treatment of acute rhinosinusitis, compared to receiving the guideline by email. The arm that included a LOK – GLEM session alone involved 35 Flemish GPs as well as 122 patient encounters for acute rhinosinusitis. No effectiveness in improving antibiotic prescription was observed: the intervention group prescribed antibiotics for 57% patients compared with 58% in the control arm. The authors conclude that there is a lack of evidence of any effect of a single LOK – GLEM session on the care for the patient.³²⁴

A KCE report on the quality development in GPs in Belgium reviewed these data and concluded that Belgian doctors do appreciate the LOK – GLEM meetings but that there is no evidence of their impact on quality of care.³²¹

EDUCATIONAL OUTREACH VISITS OR ACADEMIC DETAILING

Independent health delegates from Farmaka have also been involved in promoting prudent antibiotic prescribing through the development of educational material and outreach visits to GPs. This type of intervention is usually called 'Academic detailing' in the literature.³²⁵ Farmaka is an independent drug information centre that is conducting academic detailing at national level in Belgium to contribute to the rational prescribing of medicines. Regarding the prudent use of antibiotics, Farmaka has developed educational material in 2017, including a flow chart and a slide set. Farmaka academic detailers also used information from academic centres to do outreach visits on antibiotics using GRACE INTRO and TRACE training (cf. supra).

The effectiveness of an individual visit from a Farmaka independent health delegate has been evaluated in a cluster randomized trial in primary care in Flanders, which also involved quality circle meetings and is described above.^{326, 327} In the Farmaka arm, involving 30 GPs and 122 patient contacts,

GPs received an individual visit of the delegate, together with a flowchart containing the recommendations for management of patients with acute rhinosinusitis.³²⁷ GPs who received a Farmaka delegate prescribed 9% less antibiotics and 12% more often the first choice antibiotic (amoxicillin) than control GPs. In the arm that received both interventions, a Farmaka delegate visit and a LOK – GLEM session, GPs prescribed even less antibiotics (-12%) and selected more often amoxicillin (+93%) than colleagues who received only one intervention. However these differences were not statistically significant and the study involved small numbers of GPs and patients.³²⁷

The funding of the Farmaka independent health delegates has been stopped by the cabinet of the minister of Social Affairs and Public Health in September 2017. This also interrupted the activities related to GRACE INTRO and TRACE training.

In 2000-01, a cluster-randomized controlled before and after study assessed the effectiveness of a tailored intervention on antibiotic prescribing for acute cough, which included academic detailing.³²⁸ As the intervention included a clinical practice guideline for acute cough, an educational outreach visit and a postal reminder to support its implementation in January 2001, this evaluation has been described under the section on guidelines (see section 6.1.1.8).

POINT-OF-CARE TESTING

Most respiratory tract infections – which represent a large bulk of the visits in the ambulatory sector – are from viral origin, but clinical signs and symptoms are not specific enough to identify the likely aetiology (and thus when antibiotics are required). Prudent antibiotic prescription should ideally be based on the identification of the pathogen and of the resistance patterns, which should be available before the antibiotic treatment is initiated.²⁷⁰ Routine laboratory tests are not readily available at GP practice and results from the laboratory return with delays that prevent to guide the immediate prescription. Point-of-care testing, such as e.g. C-reactive protein (CRP) test or procalcitonin, may assist the clinician to assess the likelihood of a serious bacterial infection versus a less severe bacterial or viral infection, and the results may be obtained in a few minutes (see more under section 6.1.2.4).³²⁹ This intervention aims to reduce the clinician uncertainty by ruling



out serious infection in children.³³⁰ In clinical trials in other settings, the use of CRP and procalcitonin lowered significantly the rate of antibiotic prescribing.³²⁹

Point-of-care testing is not reimbursed at ambulatory level in Belgium, but two cluster randomised clinical trials have assessed the effectiveness of a CRP test on reducing prescription rates that was made available to a number of GPs in Flanders, among different patient groups.^{323, 329} However, these came to different conclusions.

A first cluster randomized trial was part of the European GRACE INTRO project (cf. supra). It included primary-care practices in six European countries, including Antwerp practices in Belgium. Practices were randomised into four arms: usual care, internet and on-site training in the CRP test at the point-of-care, internet training in enhanced communication skills with patients, or in both CRP and enhanced communication.³²³ Adult patients with respiratory tract infections (RTI) were recruited from February to May 2011.³³¹ The antibiotic prescribing rate (in all practices of the six countries) was lower among those with CRP training than those without (33% vs. 48%; adjusted risk ratio 0.54, 95% CI 0.42-0.69). The authors concluded that internet-based training in how to use a CRP point-of-care test achieved important reductions in antibiotic prescribing for RTI in several countries.

A subsequent publication of the same study assessed patient views with qualitative methods and revealed that most patients were satisfied with their consultation despite many not receiving an antibiotic.³³¹ In particular, patients who had initially expected antibiotics reported that they learned that these were unnecessary for their illness. This evaluation assessed both point-of-care CRP testing and enhanced communication skills. Clinicians' views were collected in another qualitative study.³³² GPs found the CRP test acceptable because it reduced diagnostic uncertainty, but difficult to incorporate in practice. They reported that the intervention helped them to prescribe fewer unnecessary antibiotics. An additional study from the same team compared GP's and patient's experiences in different datasets and reported that GPs and patients reported different views on the use of a CRP test.³³³ GPs felt that the test was useful in convincing patients to accept a no-antibiotic decision while but patients reported that this was unnecessary if a full explanation was given.

Another clinical trial was conducted under the ERNIE2 (Optimising Diagnosis and Antibiotic Prescribing for Acutely Ill Children in Primary Care) project among 131 GPs (78 practices) in Flanders in 2013-14. It assessed the use of CRP test for children with acute illness, together with parent information.³³⁰ The CRP finger prick test yielded result within four minutes. In comparison with usual care, CRP did not influence antibiotic prescribing (adjusted OR 1.01, 95% CI 0.57-1.79). The authors concluded that systematic CRP testing without guidance is not an effective strategy to reduce antibiotic prescribing for non-severe acute infections in children in primary care.

TRAINING IN COMMUNICATION SKILLS

The GRACE INTRO project (cf. supra) included e-learning in enhanced communication skills, combined with interactive booklets for patients or parents of patients.³²³ Training focus on the gathering of information on patient concerns and expectations, exchange of information on symptoms, natural disease course and treatments, as well as agreement of a management plan and providing guidance about when to reconsult. The interactive booklet is intended to use during consultations and included information on symptoms, use of antibiotics and antibiotic resistance, self-help measures, and when to re-consult.

The 2011 GRACE INTRO cluster randomised clinical trial above reported also assessed the effectiveness of training in enhanced communication skills among GPs in Flanders. Two arms included internet-based training in enhanced communication skills and the use of an interactive booklet for patients or parents of patients, which contained 'safety net' advices (alerting patients on signs and symptoms suggestive of a more severe illness).³²³ The antibiotic prescribing rate in acute respiratory tract infections was lower in practices with enhanced-communication training than in those without (36% vs. 45%; adjusted risk ratio 0.69, 95% CI 0.54-0.87). The combined intervention, point-of-care testing and enhanced communication skills, was associated with the greatest reduction in prescribing rate (adjusted risk ratio 0.38, 95% CI 0.25-0.55).



Parent views of that intervention were also assessed in another publication of the same study using qualitative methods.³³¹ Results reveal that most patients were satisfied with their consultation despite many of them not receiving an antibiotic. In particular, patients who had initially expected antibiotics reported that they learned that they were unnecessary for their illness. This evaluation assessed both point-of-care CRP testing and enhanced communication skills.

The qualitative study that assessed clinicians' views report that the communication training was received positively, as well as the booklet, which helped them to prescribe fewer unnecessary antibiotics.³³² Clinicians felt that the safety advice content was very useful, and they felt more comfortable managing patients without prescribing antibiotics when patients had access to this information to refer to.

An additional study from the same team compared GP and patient experiences in different datasets and reported that GPs and patients reported different views.³³³ The highest levels of satisfaction among patients was found in those receiving a detailed explanation from their GP with a booklet giving advice on self-care. Qualitative and quantitative data indicate a higher patient enablement for those in the communication groups who had received a booklet.

The national implementation of GRACE INTRO has not yet been evaluated.

FINANCIAL INCENTIVES FOR GPs

An increase in the fee-for-services for GPs conditional to the rational prescription of antibiotics was decided in 2003 and implemented in 2004-05 (cf. supra).³³⁴ The decision was based on an agreement between the representatives of physicians and the sickness funds ('Medico-Mut' agreement) to increase the physician fees conditional on decreasing antibiotic use. A particular emphasis was put on fluoroquinolones and broad-spectrum penicillins, in particular amoxicillin-clavulanate.³¹⁸ It also required that each LOK – GLEM would organise at least one full session to the analysis and discussion on the feed-back provided by the RIZIV – INAMI, including antibiotics. This meeting should include the comparison between prescriber profile and the recommendations and cover the therapeutic indication as well as the antibiotic choice. The LOK – GLEM could request

the assistance of specific LOK – GLEM moderators especially trained for that purpose by the scientific associations of GPs (SSMG and Domus Medica), academic centres or professional medical associations. The conditions for this additional funding were the reports of the LOKs – GLEMs describing the activities undertaken and a significant change in antibiotic prescribing behaviour. However this system was only implemented by half of the LOK – GLEM due to competing priorities. It was not further extended and only limited information can be found on that temporary measure.

A 2005 study sponsored by Bayer evaluated to which extent this temporary policy, together with individual feedback to GPs, has achieved reductions in the prescription of respiratory quinolones and in levels of resistance.³¹⁸ The study observed that the volume of fluoroquinolones (expressed in DID) used in ambulatory care nearly doubled between 1993 and 2003, partly due to the introduction of levofloxacin and moxifloxacin, before the financial intervention. When comparing pre and post-intervention periods, the study suggested that the increasing trend did not persist in the last years, i.e. in the first four months of 2004 the volume was lower than in the first four months of 2003. The study also revealed that fluoroquinolones were mainly used to treat urinary and lower respiratory tract infections, but rarely for the management of upper respiratory tract infections.

OTHER LOCAL INTERVENTIONS

A number of quality improvement projects have been implemented by GPs in professional training as part of master after master theses, and some targeted the improvement antibiotic prescribing in general practice. However, no list or description of these interventions could be identified (www.icho.be).



6.1.1.6 *Belgian interventions targeting both hospital and ambulatory sectors*

NATIONAL PLAN FOR MULTI-DRUG RESISTANT ORGANISMS

Triggered by the emergence of carbapenemase producing enterobacteria (CPE), the 2013 inter-ministerial conference Health has set up a task force to establish a national plan for multi-drug resistant organisms (MDRO). The plan has been validated by the Superior Health Council ('Hoge Gezondheidsraad' – 'Conseil Supérieur de la Santé', HGR – CSS) in 2013, and an 'Agreement protocol' on the MDRO national plan has been published in the Belgisch Staatsblad-Moniteur belge on 21/11/2013.³⁰⁷ The plan includes a section on antibiotic policy covering the different levels of care. At hospital level, it refers to existing activities, such as the role of AMT in hospitals, and at ambulatory level to the annual campaigns promoting the rational use of antibiotics, antibiotic guidelines, and regular feedback on antibiotic prescription. It describes specific activities at the level of long-term care facilities described under section 6.1.1.4. No evaluation of the implementation or impact of this plan has been found.

6.1.1.7 *Belgian interventions targeting the general public and patients*

MASS INFORMATION CAMPAIGNS

Since November 1999, national information campaigns to reduce antibiotic use have been conducted annually during winter (or influenza) season. These generally include advertisements on TV, radio and newspaper, information booklets, folders, posters and internet campaigns. The message is changed every 3-6 years and the following main messages have been communicated:³¹⁶

- 2000-03: 'Use antibiotics less frequently but better', 'Save antibiotics, they may save your life' and 'Talk to your doctor, talk to your pharmacist'
- 2004-08: 'Antibiotics are ineffective for common cold, acute bronchitis and flu'

- 2008-14: 'Please note: use only when necessary. Antibiotics don't help with the flu, bronchitis or a cold'
- 2014-18: 'Antibiotics: use them correctly and only when necessary'

The evaluation aspects that are specific to GPs are described under section 6.1.1.5.

Two studies evaluated the impact of national campaigns on the general public.^{173, 314} A first study compared the information retained by the general public from the campaigns and the expectations for antibiotic prescription in pre- (2000) and post-campaign (2001) evaluation by conducting face-to face interviews of around 1000 persons each.³¹⁴ Exact methods, scope and results are not described. After the first campaign, 46% of the general public remembered the campaign, 75% shifted opinion in favour of using antibiotics more sparingly, and expectations for antibiotic in case of acute respiratory infections decreased. A study conducted by the Socialist Sickness Fund in 2018 among its members revealed that 60% of respondents knew the existence of these campaigns, but the proportion tended to be lower in the younger (49% in the 15-29 years of age). This proportion also according to the education level, from 40% in responders with a low educational level (elementary school) to 70% in those with a high education level.¹⁷³ Among respondents with a good knowledge on antibiotics, 67% were aware of the campaign, while the respective proportion was only 41% among those that had limited knowledge.

Four studies aimed to evaluate the impact of the campaigns on antibiotic use based on reimbursement data.³¹⁴⁻³¹⁷ A time-series analysis of antibiotic reimbursement data during 1997-2002 (collected by IMS-Health) compared data during the months of the campaign months to the same months in 1999-2000 and the analysis controlled for the influence of influenza seasons using influenza-like illnesses (ILI) data.³¹⁵ The study showed that antibiotic sales were strongly correlated to the incidence of ILI, for which the systematic use of antibiotics is not indicated in the general population. After accounting for the influence of ILI, the total antibiotic sales in DDD decreased by 6.5% and 3.4% during the 2000-01 and 2001-02 winter season, respectively, compared to the 1999-2000 season. Effect was maximal at the time of the influenza peak. A similar study included 1997-2003 reimbursement data from the ambulatory sector and reported that no further reduction was



observed in DDD per 1000 inhabitants per day (DID) in 2002-03.³¹⁴ The authors suggested that the stabilisation in 2002-03 is due to an increase in the recommended dosage of amoxicillin-clavulanate and by the introduction of 'respiratory' quinolones. Overall, antibiotic use decreased by 25% between 2000 and 2003 when it was expressed in packages per 1000 inhabitants per day, compared to a 6% reduction in DID. Authors explain that the difference in reduction is due the increase in content of an average pack during the study period, from 6.9 to 7.8 DDD per pack (see section 4.1.1.3). Another study of the same group evaluated changes in antibiotic use in the ambulatory sector over 1997-2005, expressed in packages per 1000 inhabitants per day.³¹⁷ Compared to 2000 (pre-campaign), a gradual decline is observed with an average decrease of 6.9% for five years. A fourth study of the same team covered 1997-2016 antibiotic data from ambulatory case.³¹⁶ Antibiotic use expressed in DID decreased in 2000-02 but slowly increased as of 2003-04. Antibiotic use expressed in packages per 1000 inhabitants per day decreased during the first two campaigns and stabilised afterwards.³¹⁶ The difference in trends is mainly driven by bigger pack sizes. Authors noted that they cannot attribute the observed changes solely to the campaigns as a number of additional measures were taken to support appropriate prescribing. Indeed, it should be noted that ecological studies comparing pre and post-campaign and using antibiotic sale data as outcome cannot disentangle the role of each intervention on antibiotic use.

EUROPEAN ANTIBIOTIC AWARENESS DAY

The European Antibiotic Awareness Day (EAAD) is an initiative of the ECDC to increase awareness about the threat of AMR to public health and encourage appropriate antimicrobial use. It is organised every year on the 18th of November since 2008 and in each EU country. ECDC has provided all EU member states with material tested and translated in all EU languages, as well as key messages, guidance on how to organise a press conference to launch the day in their country and background material (in English only).³²⁰ A series of educational material is made available online, and ECDC communicates messages through Twitter to encourage the public to view the material posted. Belgium is usually taking that opportunity to launch the annual antibiotics awareness campaign, new interventions

(e.g. e-bug, cf. infra) and to organise scientific conferences.³²⁰ Additional information about the EAAD is included in section 6.1.2.6. No evaluation of the EAAD in Belgium was found.

ANTIBIOTIC GUARDIAN

In 2014, Public Health England launched the initiative 'Become an antibiotic guardian' in the UK to increase people's commitment to reduce AMR.³³⁵ ^{fff} This initiative invites the general population, health professionals included, to get involved in the fight against antibiotic resistance through an online pledge system. Every organisation and individual can register through a specific website, select a specific pledge and be recognised as an 'Antibiotic guardian'. The type and level of commitment vary by public group.

In 2016, Public Health England, BAPCOC and WHO Europe collaborated to translate the Antibiotic Guardian campaign in French and Dutch. The webpage translated in Dutch indicates more pledges from the public whereas the highest number of pledges in the French speaking group originates from the health care professionals. No evaluation of this initiative has been found.

E-BUG

Since 2009, an 'e-Bug' educational package has been launched in 19 European countries to encourage the knowledge on pathogens, infections and the importance of hygiene among students.

In Belgium, e-Bug has been developed by the FOD – SPF Health, Food Chain Safety and Environment and FAVV – AFSCA, in collaboration with the University of Antwerp, and with the support of the Ministry of Education of the French and German-speaking Communities. E-Bug consists of two instructional manuals: a manual for schoolchildren aged 9 to 12 years and a manual addressed to students aged 14 to 16 years. Materials are also available for teachers. Manuals are available in French and Dutch and can be downloaded for free from the e-Bug website.⁹⁹⁹ In order to evaluate the

^{fff} <http://antibioticguardian.com/french/#> or <https://antibioticguardian.com/dutch/>

⁹⁹⁹ <http://www.e-bug.eu/>



use of e-Bug packs, an online questionnaire has been developed but the results of the evaluation are not available yet.³³⁶

TANTE BIOTICA

Tante Biotica is a special edition of 'Suske and Wiske' or 'Bob et Bobette', a Belgian comic. It has been published in 2014 to educate, in a humorous way, the Belgian population about antibiotics. Tante Biotica has been distributed to all pharmacists and GPs in Belgium. Several hospitals ordered copies of the comic for their patients. The album can also be read online or ordered for free.^{hhh}

CHANGE IN REIMBURSEMENT OF ORAL ANTIBIOTICS

Since May 2017, antibiotics intended for oral administration and delivered by pharmacies open to the public have moved from category B to category C, which is the reimbursement category for drugs intended for symptomatic treatment. This measure involves nearly all antibiotics prescribed in primary care. The cabinet of the minister of Social Affairs and Public Health declared that the purpose of the measure was to counter antibiotic abuse and limit the development of resistance. No evaluation of the measure was identified. Further details are provided in section 1.1.1.1.

Since May 2018, oral quinolones have been included in Chapter IV of the list of reimbursable medicines; this means that their reimbursement is restricted to well defined indications (see further details in section 1.1.1.1). No evaluation of this recent measure has been identified. However, the project iCAREdata measures quinolone prescribing as a percentage of total antibiotic prescribing by GPs in out-of-hours primary care in Antwerp (<https://icare.uantwerpen.be/medicatie/>). Data available online (graph) suggest a drop in the proportion of quinolone among all antibiotics prescribed after May 2018.

^{hhh} <https://www.gebruikantibioticacorrect.be/nl/lees-tante-biotica-online>

ⁱⁱⁱ Hospitals that want to register for this guideline have to pay in proportion to their size (i.e. € 2 420/year for hospitals up to 400 beds, €4 235/year for

6.1.1.8 Guidelines on antibiotic prescribing

BAPCOC has invested considerable time and resources in coordinating the production of clinical guidelines for the different levels of care. Other actors such as professional groups, the RIZIV – INAMI and the HGR – CSS have produced guidelines as well, which were sometimes duplicating. Many guidelines on antibiotic prescribing for treatment and prophylaxis have thus been published, at national and local level, for the ambulatory and the hospital sector. However, stakeholders reported that insufficient support is provided from BAPCOC for guidelines, in particular in the hospital sector. The main example reported by stakeholders is the Infection guide IGGI (Infectiologiegids - Guide d'Infectiologie) made by the the Belgian Society for Infectiology and Clinical Microbiology (BVIKM – SBIMC) together with BAPCOC. Some funding was provided by BAPCOC but it was insufficient to cover all costs of the on-line version. The BVIKM – SBIMC developed the full electronic version with commercial support and is thus charging for its use.ⁱⁱⁱ A number of stakeholders also reported that BAPCOC guidelines lack access and visibility (e.g. electronic versions are difficult to find on the BAPCOC website), and that a major obstacle is the lack of implementation of these guidelines.

The major national guidelines related to prudent antibiotic use are listed in Table 44, and the few studies that evaluated guideline acceptance, compliance, applicability and perception are described below.

IN THE HOSPITAL SECTOR

In hospitals, an important step is the adaptation of existing (national or international) antibiotic guidelines to hospital-specific guidelines and protocols that takes into account local health care settings, drug formularies and resistance patterns.³³⁷ These hospital guidelines tend to be used instead of the national guidelines. The usability and applicability of the hospital antibiotic guidelines of the UZ Leuven (2005 version) was evaluated by conducting focus groups among 22 physicians in 2006-07.³³⁷ The general

hospitals from 401 to 800 beds and € 6 050/year for hospitals with more than 800 beds).



acceptance of local guidelines was high but opposing views were reported towards a number of measures. The distribution and accessibility of guidelines appeared confusing and resulted in delayed application. Supervisors, who play a role as opinion leaders, were highly influential towards residents' practice. Authors concluded that prescribers should be considered as a number of different target groups instead of a homogeneous population, and interventions should take into account these differences. Supervisors should also be made aware of how they can influence residents.³³⁷

The global PPS (see section 4.2.1.2) includes items related to guideline compliance at hospital level. The 2015 global PPS involved 63 Belgian hospitals, and reported that 80.3%, 74.2% and 83.3% of antibiotic prescriptions were compliant with the guidelines in the medical, surgical and intensive care unit wards, respectively.³³⁸

The compliance to guidelines on antibiotic surgical prophylaxis has been regularly measured by audits conducted by BAPCOC in hospitals (see section 6.1.1.3). The 2013 audit indicated that 90% (71/77) of hospitals complied with the (local) hospital guidelines for antibiotic surgical prophylaxis.²⁹⁷ The study conducted by Sciensano and described under 6.1.1.3 also assessed the compliance to guideline for surgical prophylaxis major lower limb orthopaedic surgery, based on hospital discharge data. Between 1999 and 2010, the compliance to guideline increased from 53% to 71% and the changes observed are likely to be multifactorial.²⁴

IN LONG-TERM CARE FACILITIES

The evaluation of antibiotic stewardship activities in nursing homes (see section 6.1.1.4) revealed that when guidelines were available, they were reported not to be used by 45% of respondents.³¹⁰ Although 95% respondents were aware of the existence of guidelines describing criteria to start antibiotic treatment in order to overcome diagnostic issues in the elderly, 57% reported that they do not use them in routine practice.

IN THE AMBULATORY SECTOR

A number of studies assessed the acceptability and obstacles to compliance among GPs (see also section 6.1.1.5). In a study using a lot quality assurance sampling (LQAS) method among 30 French speaking GPs, the compliance to ambulatory care guidelines (i.e. compliance for 80% patients) was 41% based on self-reporting and 59% based on assessment by independent researchers.^{171, 180} However, 32% of GPs did not know the guidelines. Authors concluded that official guidelines and recommendations have only a limited impact on the actual prescribing behaviour.¹⁸⁰ Focus group discussions in these GPs also revealed that reasons for not following guidelines were that the formulation of guidelines was driven by economic interests (cost-saving) and that most guidelines were not possible to apply in real life practice.¹⁶⁴

**Table 44 – National guidelines for prudent antibiotic prescription and use at human level**

Guideline name	Date	Target group	Url and implementation	Coordination	Funding
Belgian guide for the treatment of infections in ambulatory care Last version 2012. Updated version expected in 2019.	2006, 2008, 2012 (2017)	GPs and specialists in ambulatory care	Sent to all GPs in 2006 and in 2008 http://www.cbip.be/legacy_assets/antibioticagids-fr.pdf	BAPCOC	BAPCOC
The rational use of antibiotics in children in ambulatory care. RIZIV – INAMI consensus meetings	2016	GPs and specialists in ambulatory care	https://www.riziv.fgov.be/fr/publications/Pages/reunions-consensus-rapports-jury.aspx#.WddF_tJrzxA	NCQP, RIZIV – INAMI	RIZIV – INAMI
Recommendations for the treatment of infections at the hospital level³⁷	2017	Hospital prescribers	http://organesdeconcertation.sante.belgique.be/sites/default/files/documents/bapcoc_guidelineshospita2017_sbimc-bvikm_fr_v1.pdf	BAPCOC and BVIKM – SBIMC	BAPCOC
Infection guide (Infectiologiegids – Guide d'Infectiologie or IGGI)	2017	Any prescribers	Same as guide above but more details, with login on BVIKM – SBIMC website http://www.bvikm.org/home-fr Paying access	BVIKM – SBIMC	BAPCOC (€50 000), BVIKM and access paid by users
Strategy for the prescription of oral antibiotics for most frequent infections in ambulatory practice in patients without comorbidity	2009	GPs and specialists in ambulatory care	Synthesis of the BAPCOC 2008 guidelines https://www.riziv.fgov.be/SiteCollectionDocuments/feed-back-antibiotiques-tableau-guide-bapcoc.pdf	RIZIV – INAMI	RIZIV – INAMI
Guidelines for the control and prevention of MRSA transmission in Belgian hospitals (SHC 7725)	2005	Hospital prescribers	https://www.health.belgium.be/fr/node/21217	HGR – CSS	HGR – CSS

GP: general practitioner; BAPCOC: Belgian Antibiotic Policy Coordination Committee; MRSA: Methicillin-Resistant Staphylococcus Aureus; NCQP: National Council for Quality Promotion; RIZIV – INAMI: National Institute for Health and Disability Insurance; BVIKM – SBIMC: Belgian Society for Infectiology and Clinical Microbiology; HGR – CSS: Superior Health Council



In Flanders, a cluster-randomized control study involving 85 GPs and adult patients with acute cough in 2000-01 to assess the effect of a clinical practice guideline for acute cough, introduced together with an educational outreach visit and a postal reminder with key messages.³²⁸ The prescribed antibiotics were more in line with the guideline in the intervention group compared to the control group (adjusted odd ratio 1.90, 95%CI 0.96-3.75). A quasi experimental design was also applied in two out-of-hours Flemish organizations involving 134 GPs (in Turnhout and Antwerp) to assess the compliance to guidelines on lower urinary tract infections. A multi-faceted 16-week intervention included an e-mail sent to GPs highlighting the core recommendations of the national guideline, followed by e-mail reminders.³³⁹ The proportion of appropriate prescriptions in the intervention group increased from 27% to 69%, but decreased afterwards to 41%. Authors concluded that simple, multifaceted intervention for treatment of lower urinary tract infections during out-of-hours care may improve the quality of antimicrobial prescribing but the improvement may not be sustained in the longer term.

A study assessed the compliance of guidelines for lower urinary tract infections in out-of-hours primary care in nine EU countries. In Belgium, guideline compliance in 100 patients was 37%.³⁴⁰ Another study assessed the compliance to guidelines for sexually transmitted infections among GPs in Flanders. The proportion of cases treated with recommended antibiotics rose from 13% in 2009 to 56% in 2013, but numbers of cases were small.³⁴¹

6.1.1.9 *Belgian interventions that are under discussion in Belgium*

RECOGNITION OF THE INFECTIOLOGY & MEDICAL MICROBIOLOGY SPECIALISATION

The medical specialisations in infectiology and/or medical microbiology are not recognized in Belgium. However, these medical specialties are mentioned in the royal decree of 2008 as a prerequisite for the composition of the antibiotic management teams in hospitals. Furthermore, European standards for these training have been agreed at European level as early as 1999 by the European Union of Medical Specialities (EUMS) Section of Infectious Diseases and the Section of Medical Microbiology, respectively. They consist in at least 3-year of post-graduate specialty training in addition to a common trunk (e.g. internal medicine).^{jjj, kkk} This issue was also acknowledged by the ECDC visit to Belgium, which highlighted that the vast majority of EU countries have already recognised these specialties (see section 9.1).⁷⁶ The ECDC reporters related that gap with the fact that doctors with the appropriate competence in the area of infectious diseases or clinical microbiology, who give advice on antimicrobials, feel that their role is not acknowledged and does not count for the purposes of reimbursement.

This request to recognise infectiology and medical microbiology as medical specialisations has been regularly discussed in official working groups at national level, but no decision has been officially issued yet. In 2013, a working group of the National Council of Hospitals has discussed the role of infectiology in hospitals on the request of the cabinet of the minister of Social Affairs and Public Health, i.e. the presence of internists and/or paediatricians with proven expertise in infectious diseases with a 24/24 hours and 7/7 days availability to provide advice, as well as the presence of clinical biologists with an expertise in that field.³⁴² The working group has concluded that this is totally related to these medical specialisations, and that the question should be submitted again to the Superior council of Medical Specialists and

^{jjj} https://www.uems.eu/_data/assets/pdf_file/0004/72265/ETR-in-Infectious-Diseases-2018-corrected-1.pdf

^{kkk} https://www.uems.eu/_data/assets/pdf_file/0003/52527/2017.34-UEMS-MM-curriculum-submitted-European-council-2017.09.21.pdf



General Practitioners. A request has been submitted to that committee in 2017 but no response has been identified.^{III}

ELECTRONIC TOOLS TO ADVISE ON TREATMENT

In Belgium, no Computerized Decision Support System (CDSS, i.e. computer applications designed to aid clinicians in making diagnostic and therapeutic decisions in patient care) system has been introduced at large level. EBM PracticeNet has integrated evidence-based clinical guidelines in the electronic medical record systems of GPs.

Prescribers in Belgium can use the electronic prescription (e-prescription) using specific software. In May 2018, e-prescription was aimed at becoming compulsory and generalized in all practices but the implementation has been postponed until January 2020. However, the system does not foresee to include information on the patient diagnosis and this preclude the use of e-prescription as a tool to aid decision making. A large number of stakeholders consulted during this study stated that e-prescription represents an important opportunity for a prudent use of antibiotics. It may invite prescribers to justify antibiotic prescription (and use of specific antibiotics), provide direct access to decisional tools related to the indication such as recommended schedule, and provide them a rapid feedback on their personal antibiotic prescription practices (see chapter 7).

The BAPCOC working group on ambulatory care has included in its 2014-19 plan the objective to develop an electronic version of the outpatient anti-infective therapy guidelines for Belgian healthcare professionals and to integrate it in electronic medical records.⁷⁷

Some Belgian hospitals are also considering or testing the use of CDSS at ward level, but no evaluation has been identified yet.

DELAYED PRESCRIPTION

One of the strategies to reduce antibiotic prescribing in ambulatory care is to provide a prescription, but to advise the patient to wait and use the antibiotic only if the symptoms have not resolved or deteriorate by a certain period of time (see also section 6.1.2.4).³⁴³ The prescription would remain valid for a number of days. This strategy may address the situation where clinicians are not feeling confident of not prescribing an antibiotic to a patient with an initially uncomplicated viral disease such as a respiratory infection. Delayed prescription has been discussed at RIZIV – INAMI and BAPCOC level since a few years but no consensus has been found on its implementation. Two main problems are raised: it shifts the responsibility from the physician to the patient and it may increase the risk of leftovers if the prescription is bought for future use.

Delayed prescription is sometimes used in practice in Belgium, though not being encouraged. A multi-country cohort study (within the GRACE study) evaluated the use of delayed prescription in general practices of 13 EU countries in 2016-17, and included the Antwerp region.³⁴⁴ In Antwerp practices, 4.2% of patients with acute cough received a delayed antibiotic prescription, and the median delay period was 3 days. Less than half of them used the antibiotics.

6.1.1.10 Summary and discussion

As described above, overall more than 30 different interventions have been or are conducted in Belgium to promote the prudent use of antibiotics in the human sector, in addition to numerous guidelines on antibiotic prescribing. Around half of those target the hospital sector and include various antibiotic stewardship activities conducted by the antimicrobial management teams of each hospital, as well as training in antibiotic management, feedback to prescribers on antibiotic use and financial incentives. Around ten interventions target the prescribers of the ambulatory sector, mostly general practitioners (GPs), and involve feedback to prescribers, training, peer education, information campaigns, and availability of point-of-care testing in

^{III} https://organesdeconcertation.sante.belgique.be/sites/default/files/documents/2018-3_rapport_annuel_2017_fr.pdf



a limited number of GPs. Around six interventions target the general public and cover mostly information activities. Only a limited number of interventions address the prudent use of antibiotics in nursing homes.

A number of these interventions have been evaluated in Belgium. However, most evaluations covered the implementation aspects (process and output indicators) such as the activities implemented and the antibiotic volume, and not the impact on human health (i.e. AMR prevalence, incidence and mortality). The impact of these interventions is difficult to assess with routine data and many Belgian studies used a before-after design (i.e. comparing the antibiotic use before and after the intervention) to assess the impact of an intervention. This method generates a lower level of evidence, as any improvement in antibiotic use and human health over time may be influenced by many other temporal changes (and confounders), and thus not be attributed to the specific intervention. For instance, an increase in recommended dosage of a common antibiotic during the same period would tend to underestimate the impact of an evaluation targeting prudent antibiotic use as it would result in higher antibiotic use (measured in DDD) in the period after the intervention. Furthermore, antibiotic sale data at population level do not inform on whether antibiotics were used prudently or appropriately.

The lack of decline of the overall antibiotic use in Belgium in the last decade, in both ambulatory and hospital sectors (see sections 4.3.1), does not suggest an overall impact on the amount of antibiotic use. A few studies provided a better level of evidence as they used more robust designs (e.g. cluster randomised trial), more specific outcomes and/or an appropriate comparison group. However, only few of them identified a positive impact of specific interventions. At the ambulatory care level, a cluster randomised trial found a significantly positive impact in GPs who received training in enhanced communication skills, or access to point-of-care testing; the combination of both interventions was the most effective. At hospital level, the temporary implementation (1997-2006) of a fixed lump sum for antibiotic prophylaxis by surgical procedure resulted in a more rational use of antibiotic prophylaxis after the financial measure, and sharp decline in antibiotic expenses.

It should be noted that a majority of initiatives focused on knowledge and awareness raising (e.g. media campaigns, educational programmes, peer education, training, feedback on prescriptions). However, a number of

qualitative studies highlighted that changes in knowledge did not translate into changes in behaviour among prescribers, due to a number of socio-cultural and individual factors, including diagnostic uncertainty.

A number of promising interventions, such as the use of e-prescription to guide antibiotic decisions, are still under discussion in Belgium.

Key messages

- **Overall, more than 30 different interventions have been (or are) conducted in Belgium to promote the prudent use of antibiotics in the human sector. The majority of interventions targeted prescribers from the hospital and ambulatory sectors, or the general public.**
- **In addition, considerable efforts and resources have been invested into the production of clinical guidelines for the different levels of care. As many actors have been involved, some level of duplication exist between guidelines. Limited resources were invested into the implementation of guidelines.**
- **A small number of activities have been conducted to address prudent antibiotic use in long-term care facilities such as nursing homes, and they were limited in scope.**
- **A number of these interventions have been evaluated, but only very few studies assessed their impact on human health (i.e. AMR prevalence, incidence and mortality). Many studies used changes in antibiotic volumes as proxy outcome for prudent use or changes in human health. Most studies used the pre-intervention data as comparator (before-after design), but they are less robust as improvement in antibiotic use and human health over time may be due to other temporal changes than the intervention.**
- **The first interventions were followed by a decrease in overall antibiotic use in Belgium. However, the increase in antibiotic use in the last decade, in both ambulatory and hospital sectors, does not suggest a lasting overall impact of these interventions on the amount of antibiotic use. Furthermore, it does not inform on whether antibiotics were used prudently or appropriately.**



- A few studies of higher quality, using a more robust design, specific outcomes and/or an appropriate comparison group, assessed single interventions. A positive impact on prudent antibiotic use was observed when GPs received a training in enhanced communication skills, access to point-of-care testing or both interventions, and among hospital prescribers during the temporary implementation (1997-2006) of a fixed lump sum for antibiotic prophylaxis by surgical procedure.
- The majority of interventions focused on knowledge and awareness raising but evaluations suggest that changes in knowledge did not translate into changes in behaviour among prescribers, due to a number of socio-cultural and individual factors, including diagnostic uncertainty.

6.1.2 Interventions that have been implemented and evaluated elsewhere

6.1.2.1 Search strategy

We performed a pragmatic literature review of interventions to promote the prudent use of antibiotic performed outside Belgium. Details about the methods and search strategy can be found under Appendix 3.1. We retained RCTs and observational studies published in English, French or Dutch from January 2000 to July 2018 and performed in EU/EEA countries. Information on the 65 references whom the whole text was considered in this report are included in Appendix 3.2. Forty-three (43) references were retained for the report.^{272, 323, 343, 345-383} We present below an overview of interventions performed at the hospital and ambulatory level. In section 6.1.2.7 the experience of France is elaborated.

6.1.2.2 Interventions at hospital level

ANTIMICROBIAL MANAGEMENT TEAMS IN HOSPITALS

In the Netherlands, mandatory antimicrobial stewardship teams (A-teams) are implemented in hospitals. The team usually consists of an internist-infectiologist, a microbiologist, a pharmacist, and an IT-specialist. Some key elements of the A-team strategy are: antimicrobial vigilance alert (daily monitoring of used antibiotics), audit-feedback, and an intravenous (IV)-oral switch programme. In 2017, a synthesis of expert opinions highlighted the high level of evidence of the cost-effectiveness of the A-teams. For instance, a Dutch hospital estimated a €40 000 hospital-wide cost-saving over a 12-month period after introduction of the A-team. Implementation of the A-team resulted in 25% less prescription of last resort antibiotic, modification of more than half of all antibiotic prescriptions, and a 1-day earlier intravenous to oral switch.³⁵⁴ A survey was conducted in 80 Dutch hospitals in 2017 and 64 hospitals responded to the questionnaire, indicating that 60 (94%) hospitals had an A-team, corresponding to a considerable increase compared to 2016 (42%).³⁸⁴ The time dedicated by the A-team to antimicrobial stewardship-related activities was a mean of 19.8 hours per week in 2017.³⁸⁴

In France, antimicrobial multidisciplinary teams, consisting in a pharmacist and a physician specialised in infectious diseases, were implemented in 2007. A cluster-controlled trial conducted in one university hospital evaluated the medium to long-term effect (2 to 7 years) of the antimicrobial multidisciplinary team on the use of antibiotics and costs savings.³⁵⁸ Authors noted an overall reduction of antibiotic use that amounted to 33% in the short term (between 2007 and 2009) but only 11% in the long-term (between 2009 and 2014). The main decreases concerned fluoroquinolones and glycopeptides. Authors also highlighted that cost fell by 10.5% in the intervention group versus 5.7% in the control group between 2009 and 2014.³⁵⁸ The impact of the advisor time spent on antibiotic prescriptions audit was evaluated in a longitudinal multicentre study that included 74 hospitals from south-western France. Results show that time devoted by the antibiotic advisor to audit activities was associated with a decrease in fluoroquinolone use (Odds Ratio (OR) 5.7, 95% CI 1.4-22.9).³⁷⁹



RESTRICTED LISTS OF ANTIBIOTICS

The restricted list of antibiotics, defined as 'removal of specific antibiotics from the formulary or restriction of use by requiring preauthorisation by a specialist (infectious diseases or medical microbiology) or allowing use for only 72 hours with mandatory approval for further use' was evaluated in a systematic review that included RCTs and observational studies from 1979 to 2014.²⁷² The overall effect on mortality was limited and non-significant whereas two observational studies noted a significant reduction of length of stay (LOS). All (except one) studies showed reduced costs, which were significant in four studies. Overall restrictive measures effectively reduced the amount of monthly prescribed DDD of restricted antibiotics, significantly lower than without restriction. Resistance rates for restricted antibiotics were significantly decreased across a wide variety of infective agent and drug combinations. A few studies reported increased resistance rates for non-restricted antibiotics.²⁷²

PROMOTION OF RAPID PARENTERAL TO ORAL SWITCH THERAPY

A systematic review included 18 studies assessing the switch from intravenous to oral therapy, of which 11 were RCTs.²⁷² Nevertheless, the quality of evidence was low because of small sample sizes and high risk of bias. Although four studies showed a non-significant beneficial effect on mortality rate and one showed a non-significant negative effect, the overall effect on mortality rate was non-significant. Two observational studies and five RCTs showed significant effects on reducing LOS, whereas costs were reduced in three observational studies and eight RCTs (two and one had significant results, respectively).²⁷²

DE-ESCALATION OF THERAPY

Among the 25 studies included in the systematic review, 17 showed decreases of mortality rate (7 being significant) and the relative risk reduction (RRR) for mortality across studies was 56% (Risk Ratio (RR) 0.44, 95% CI 0.30-0.66).²⁷² Ten studies reported on LOS, of which nine suggested a decreased duration (two showed significant effects) and among the 13 studies reporting on costs, 11 showed savings when comparing de-escalation therapy with unmodified therapy (five reported significant effect).²⁷²

AUDIT AND FEEDBACK TO HOSPITAL PRESCRIBERS ON ANTIBIOTIC USE

Audit and feedback interventions have been defined by the Cochrane Review Group of Effective Practice and Organisation of Care (EPOC) as: 'a summary of health workers' performance over a specified period of time, given to them in a written, electronic, or verbal format'. The summary may include recommendations for clinical action.^{mmm, 385} This strategy is based on the belief that healthcare professionals are willing to modify their practices when they receive performance feedback showing that their clinical practice is inconsistent with a desirable target.²⁹⁴ Audit and feedback should be distinguished from post-antibiotic prescription review, in which the management of specific patients are discussed with the treating physician, and is described below.

A systematic review published in 2009 estimated the effect of audit and feedback interventions in improving prescription practices. It encompassed all types of prescriptions (not only antibiotics) and demonstrated that among seven of the 12 highly-quality included studies, audit and feedback interventions showed clear effects in improving prescribing. Three of the studies showed partial effectiveness with short-term, modest effects.³⁴⁶

^{mmm} Effective Practice and Organisation of Care (EPOC). EPOC Taxonomy; 2015. Available at: <https://epoc.cochrane.org/epoc-taxonomy>



POST-PRESCRIPTION REVIEW

A post-prescription intervention, or post-antibiotic prescription review (PAR, see section 6.1.1.3 for PAR in Belgium), consists in a systematic revision of the antibiotic prescription at specific time (days) after treatment initiation, usually conducted by the infectious disease physicians specialised in antibiotic stewardship strategy.³⁵⁷ A systematic revision of the antibiotic prescription at day 1, 3 and 4 of treatment was evaluated in a multicentre RCT (the so-called 'ANTIBIOREF' trial) performed in 2010 in France.³⁵⁷ This study estimated the impact of the post-prescription review on the appropriateness of antibiotic therapy (using composite score) and treatment duration. Authors found that the treatment was significantly more frequently appropriate in the intervention group compared to the control group (44.7% vs. 28.5%, $p=0.008$) and that antibiotic treatment duration was lower in the intervention group than in the control group (median 7 days vs. 10 days; $p=0.003$).³⁵⁷

Another type of PAR is the bedside consultation defined as 'a formal consultation by an infectious disease specialist leading to written comments and advice on treatment based on physical examination and review of medical records'.²⁷² A systematic review concluded that the overall effect of bedside consultation on mortality was not significant.²⁷² Three studies included in the systematic review reported the effect on hospital LOS: one showed a decrease in LOS, two showed an increase (one being significant). The two studies that reported on costs were contradictory.²⁷²

In 2015, a Dutch hospital implemented a type of post-prescription review consisting in a face-to-face day 2 case audit.³⁸⁶ The intervention was conducted as follows: the hospital pharmacist sent an automatic email alert to all stewardship members 48 hours after start of antibiotic therapy. This then triggered a case-audit: a stewardship member visited the ward to discuss the patient's therapy with the bedside physician. Together, they decided on further treatment based on diagnostics and local guidelines. The cost-effectiveness of this intervention has been evaluated at a urology ward.^{354, 387} They observed a significant reduction in the number of antibiotic prescriptions and a decrease in the LOS of 6.2 days (95 % CI 5.59-6.81) for patients with case-audits compared to the historic cohort (7.57 days, 95% CI 6.92-8.21; $p=0.02$). They also observed a decrease of the antibiotic use for patients with case-audit from 8.17 DDD/patient (95% CI 7.10-9.24) to 5.93

DDD/patient (95% CI 5.02-6.83, $p=0.008$).³⁸⁷ For this specific patient group admitted to an urology ward and consulted on day 2 by the A-Team, they also estimated total savings of €60 306 after one year for this single department, leading to a return on investment of 5.9.³⁸⁶

POINT-OF-CARE TESTING IN HOSPITALS

A systematic review and meta-analysis assessed the safety and efficacy of using procalcitonin (PCT) for starting or stopping antibiotics in acute respiratory tract infections (RTIs).³⁴⁷ Authors did not observe difference in all-cause mortality in the PCT group patients compared to the control patients (5.7% vs. 6.3%, OR 0.94, 95% CI 0.71-1.23). This was consistent across clinical settings and RTI diagnoses. They also observed a significant lower risk for treatment failure in PCT-treated patients compared to control patients (19.1% vs. 21.9%, OR 0.83, 95% CI 0.71-0.97), and total antibiotic exposure duration was significantly reduced overall, from 8 to 4 days.³⁴⁷

A number of other European RCTs concluded that using PCT reduced the duration of antibiotic treatment and the proportion of patients under antibiotic treatment, but the effect on mortality was conflicting across studies. Four RCTs studied the impact of using PCT as intervention to promote the prudent use of antibiotic at hospital level. In a RCT performed in Switzerland early 2000's that included 243 patients, the authors concluded that the proportion of antibiotic prescribed was significantly lower in the PCT group than in the standard group (44% vs. 83%, $p<0.0001$) and that the duration of treatment was significantly lower in PCT group than in standard group (10.9 days vs. 12.8 days, $p<0.0001$).³⁶⁶ No differences in clinical outcome between PCT and the standard group was observed.³⁶⁶ Another Swiss RCT that included 68 patients also noted an effectiveness of using PCT to promote the prudent use of antibiotics, as PCT guidance resulted in a 4-day reduction in the duration of antibiotic therapy ($p=0.003$) and a smaller antibiotic use ($p=0.0002$).³⁶¹ A RCT performed in three Dutch university hospitals that included 1574 patients also concluded the effectiveness of PCT as intervention to promote prudent use of antibiotic in hospital.³⁵⁹ The median use of antibiotics was significantly lower in the PCT group than in the standard group (between-group difference 1.22, 95% CI 0.65-1.78; $p<0.001$), the duration of treatment was also significantly lower in the PCT group (5 days vs. 7 days, absolute difference 1.22 days, IQR 0.65-1.78,



$p < 0.001$) as well as the mortality at 28 days (PCT 20 vs. standard 25%, absolute difference 5.4%, 95% CI 1.2-9.5%, $p = 0.0122$).³⁵⁹ Finally a RCT performed in Denmark in a university hospital on 120 patients with acute exacerbation of chronic obstructive pulmonary disease (COPD)³⁶⁵, concluded that the proportion of patients using antibiotics for ≥ 5 days within the 28-day follow-up was lower in the PCT group than in the standard group (41.9% vs. 67.2%, $p = 0.006$) and that the duration of antibiotic exposure was lower in PCT group than in the standard group (3.5 vs. 8.5; $p = 0.0169$). No apparent differences in the mortality rate and adverse outcomes between PCT and standard group were observed.³⁶⁵

OTHER RAPID DIAGNOSTIC TESTS

The effect of using multiplex Polymerase Chain Reaction (PCR) to promote the prudent use of antibiotic has been assessed in two RCTs. Multiplex PCR is a variant of PCR in which two or more target sequences can be amplified and has the potential to produce considerable savings of time and effort in the laboratory. One RCT was conducted in London between January and July 2015, and concluded that multiplex PCR was not associated with reduced LOS, but reduced the turn-around-time from 39.5 h to 19.0 h ($p < 0.001$).³⁶⁷ The second RCT³⁶⁴, conducted in Switzerland between March 2012 and November 2013 on 89 patients suffering from bacteraemia, evaluated the impact of rapid determination of MRSA infections to improve early targeted antibiotic prescribing. The authors concluded that median time from Gram stain to the transmission of methicillin-susceptibility results was significantly lower for the triplex real-time PCR group than for the standard group (3.9 hours vs. 25.4 hours, $p < 0.001$) and that median time from Gram stain to targeted treatment was significantly shorter in the intervention group when considering *S. aureus* only (5 hours vs. 25.5 hours, $p < 0.001$). When standard susceptibility testing was completed (based on culture), 85.4% of the patients in the intervention group had already received targeted therapy compared to 56.1% in the control group ($p = 0.004$). The authors concluded that rapid determination of MRSA was accurate and reduced significantly the time to targeted antibiotic therapy in the subgroup of *S. aureus*, thereby avoiding unnecessary exposure to vancomycin.³⁶⁴

COMPUTER-ASSISTED DECISION SUPPORT TOOL

In France, a computer-assisted decision support was designed to provide clinicians with essential guideline-based information concerning the treatment of infections, the use of antibiotic agents and microbial diagnostics in the intensive care units.³⁷⁵ The impact of this intervention was assessed in a prospective cohort study established in five emergency units. The evaluated outcomes were included the adherence to guideline, antibiotic-free days and mortality rate and were evaluated during three post-interventions periods (period 1 (p1), period 2 (p2) and period 3 (p3)). Results reveal a net increase of 10% in guideline adherence during the 5-year observation period. The number of antibiotic-free days increased over time, starting from 30% of all intensive care unit days (p1) and finally achieving 42% (p3, $p < 0.01$). Among the 1346 patients included, authors also observed that the mortality rate was significantly lower in patients for whom physicians had a guideline adherence higher than 70% (12.3%) than for whom physicians had a guideline adherence lower than 70% (8%, $p = 0.014$).³⁷⁵

QUALITY INDICATORS

In the Netherlands, a checklist included quality indicators, i.e. blood cultures, cultures of suspected site of infection, guideline adherence, documented antibiotic plan, adapt therapy when culture results become available, intravenous to oral switch. Education, feedback and reminders were organized for the participating physicians. This intervention was assessed by a cluster RCT in eight hospitals to estimate the impact of the implementation of the checklist on LOS and appropriate use of intravenous antibiotic treatment.³⁵⁶ Although the authors did not observe change in LOS after implementation of the checklist, they observed that antibiotics were used more appropriately according to quality indicators after the introduction of the antibiotic checklist. The percentage of patients with a qualitative sum score above 50% increased significantly by 18.7 % ($p < 0.001$).³⁵⁶



COMBINATION OF INTERVENTIONS AT HOSPITAL LEVEL

A systematic review and meta-analysis published in 2017 estimated the effect of persuasive interventions accompanied with restrictive measures on the prescribing practices for hospital inpatients.³⁴⁵ Persuasive interventions, defined as 'using communication to induce positive or negative feelings or to stimulate action' included feedback and audit, educational outreach and circumstantial reminders. Restrictive measures, defined as 'using rules to reduce the opportunity to engage in the target behaviour or increase the target behaviour by reducing the opportunity to engage in competing behaviours', included selective reporting of laboratory susceptibilities that require prior authorization, therapeutic substitution and automatic stop orders. The review observed that more inpatients were treated according to antibiotic prescribing policy in the intervention group compared to no intervention (Risk Difference (RD) 15 %, 95% CI 14%-16%, 29 RCTs), that the duration of antibiotic treatment decreased by 1.95 days (95% CI 2.22-1.67, 14 RCTs) in the intervention group and that the risk of death was similar between interventions and control groups (~11 % in both arms). This also suggests that antibiotic use can be reduced without adversely affecting mortality (RD 0%, 95% CI 1%-0%, 28 RCTs). Persuasive interventions coupled with restrictive measures also reduced LOS by 1.12 days (95% CI 0.7-1.54 days, 15 RCTs) and persuasive measures that included feedback were more effective than those that did not. Although the review concluded that restrictive interventions enhanced the effectiveness of the intervention and increased compliance with antibiotic policies with a high level of evidence, they also highlighted the need of additional research to understand the unintended consequence of the use of restrictive interventions to promote prudent use of antibiotic. Indeed, only two RCT retained in the review included restriction interventions, and one stopped early because of delay in start of treatment. Two non-randomised trials that included restrictive interventions raised concerns about the delay in time to first antibiotic dose associated with restrictive interventions.³⁴⁵

6.1.2.3 Interventions in nursing homes

In London nursing homes, a novel antimicrobial stewardship tool (pre-printed) included a first part entitled 'Initiation of treatment' that had to be completed before administration of the first dose and a second part entitled 'review of treatment' started 48–72 h after treatment initiation.³⁸¹ Both parts were divided into subsections or 'good practice points' in relation to antimicrobial prescribing, administration and monitoring in line with prior Department of Health (England) recommendations. In 2010, a prospective cluster randomized control pilot study estimated the impact of this intervention on systematic antibiotic use in 30 Nursing homes in London. 1628 residents were included (general practitioners and nurses). Antibiotic prescriptions for infection decreased by 4.9% in the intervention group (95% CI 1.0-8.8, $p=0.02$) compared with a significant increase of 5.1% in the control group (95% CI 0.2-10.2, $p=0.04$).³⁸¹

A systematic review published in 2013 assessed various interventions to improve the quality of antibiotic prescribing in Long-Term Care Facilities (LTCF). It included four RCTs from Canada (2), Sweden or USA.³⁵² Three studies directed educational material and sessions at physicians and nurses, with one of the three studies providing prescribing feedback as well. The fourth study provided educational material and prescribing feedback for physicians only. Due to the mixed and modest effects of the intervention, none intervention was evaluated as being successful. However authors concluded that multifaceted intervention involving small group educational sessions and the provision of educational material was generally acceptable to nurses and physicians in LTCF, and the involvement of local consensus procedures when developing guidelines and interventions may improve the success of intervention in LTCF.³⁵² Overall, authors noted that there is currently little evidence on the effectiveness of interventions to promote the prudent use of antibiotics in LTCF, mostly in academic or hospital-affiliated settings.³⁵²

Another systematic review with similar objectives as the one described above,³⁵² came to the same conclusion,³⁸⁸ confirming that there is a need for further evaluation to characterize effective antimicrobial stewardship for long-term care facilities .



6.1.2.4 Interventions targeting prescribers at ambulatory care level

POINT-OF-CARE TESTING IN AMBULATORY CARE

A systematic review estimated the impact of CRP as point-of-care testing to guide prescription of antibiotics in patients with acute respiratory infections in primary care.³⁵³ The review included six RCTs (3 RCTs and 3 cluster RCTs) and showed mitigated results of the intervention. Although pooled effect (RR) of the six RCTs showed an overall significant reduction of the antibiotic use in the CRP group versus standard of care (RR 0.78, 95% CI 0.66-0.92), the high level of heterogeneity requires to interpret results with caution. Authors performed meta-analyses stratified by study design (RCT vs cluster RCT) to address that heterogeneity. The three RCTs showed a non-significant and limited reduction of the use of antibiotic treatment in the CRP group versus standard of care group (pooled RR 0.90, 95% CI 0.80-1.02) whereas the three cluster RCTs showed a significant reduction of the use of antibiotic treatments in the CRP group (pooled RR 0.68, 95% CI 0.61-0.75). No differences in mortality and clinical recovery rate were observed, yet there was an increase in hospitalisations in the CRP group in one study.³⁵³

Three Dutch RCTs assessed the effect among GPs of CRP testing and training in enhanced communication skills on antibiotic prescribing in respiratory infections.^{372, 370, 371} The first two RCTs are included in the systematic review of Aabenhuis presented above.³⁵³ The GPs were given devices to test for CRP (Nycocard II Reader), according to the manufacturer's instructions. A result was available within three minutes, using a drop of blood obtained by finger pick. GPs were given guidance on how to use the test results within the consultation during a 30 minutes practice based training session delivered by the study team. The enhanced communication skills intervention was built around 11 key tasks.^{370, 389} In the first study (2009) that included 40 GPs, GPs in the CRP group prescribed antibiotics to 31 % of their patients compared with 53 % in the no test group ($p=0.02$); clinicians in the combined group (CRP and communication) prescribed antibiotics to 23% of their patients.³⁷² In the second study (2010), which included 32 GPs, only the CRP-assisted intervention was evaluated, but using another reader of the CRP result (Orion Diagnostica). It was

observed that patients in the CRP group used fewer antibiotics (43.4%) than control patients (56.6%) after the consultation (RR 0.77, 95% CI 0.62-0.99). The medical recovery was similar across groups and satisfaction was higher in patients in the CRP group.³⁷⁰ The third study was a 3.5 years follow-up of the first study,³⁷² and concluded that the CRP intervention did not demonstrate a long-term impact on the antibiotic prescription rate.³⁷¹

Another RCT (combined with a qualitative study) conducted in the UK estimated the impact of CRP point-of-care on antibiotic prescription in 54 acutely ill children.³⁷⁴ The study found no significant difference in antibiotic use between those tested or not with CRP point-of-care at consultation (CRP 38.5% vs. not CRP 32.1%, $p=0.627$) but a significantly higher antibiotic use during the 10-day follow-up period in children from the CRP group (CRP 35.3% vs. not CRP 5.3%, $p=0.023$). No significant difference in the number of hospital admissions, additional testing or re-consultations was observed between those tested or not with CRP point-of-care at consultation and during the 10-day follow-up. Semi-structured interviews revealed no major concern about the test from parents and nurses. The GPs and some parents also emphasised that a CRP result should be part of an overall assessment. However authors warn that the safety of that strategy should be assessed before widespread implementation, as studies suggest that serious infections can be present in children with CRP levels as low as 5mg/L, especially in the early stages of the illness.³⁷⁴

EDUCATIONAL ACTIVITIES FOR AMBULATORY PRESCRIBERS AND PATIENTS

In 2007, a RCT was published which estimated the effectiveness of a Wales (UK) educational programme ('Stemming the Tide of Antibiotic Resistance' (STAR)) on the total numbers of oral antibiotics dispensed and on the re-consultations, admissions to hospital, and costs.³⁷³ The programme focused on GPs ($n=263$) and consisted of various learning methods and topics. The main findings were a reduction of 4.2 % (95% CI 0.6-7.7 %, $p=0.02$) in overall oral antibiotic prescription in practitioners who received the STAR training relative to the control group. No significant difference was observed between the intervention and control groups in the number of admission to hospital or consultations, and there was a non-significant 5.5% reduction in the cost of



dispensed antibiotics in the intervention group compared with the control group (-0.4%-11.4%, $p=0.07$).³⁷³

In 2013, a systematic review assessed the effectiveness of parent education and clinician behaviour change interventions on the proportion of antibiotic prescriptions for RTIs.³⁴⁹ The systematic review concluded that 8 of the 10 interventions that combined parent education and clinician behaviour change decreased antibiotic prescribing rate between 6% and 21 %.³⁴⁹

In 2005, a systematic review assessed the effectiveness of professional educational interventions in improving the selection, dose and treatment duration of antibiotics prescribed by healthcare providers in the ambulatory setting and the impact of these interventions on reducing the incidence of antimicrobial resistant pathogens.³⁴⁸ The review observed no or only small changes in prescribing with the use of printed educational materials for prescribers. Educational meetings for prescribers appeared to be more effective than didactic lectures and educational outreach visits to prescriber resulted in mixed results.³⁴⁸

In an RCT in England that included 1581 general practitioners, authors also concluded that education material for patients had no significant impact on antibiotic prescription rate.³⁶³ Two systematic reviews also concluded that passive information, in the form of waiting room educational materials, yielded no benefit for prudent use of antibiotic.^{348, 349}

RESTRICTING THE TYPE OF ANTIBIOTICS BY FINANCIAL MEASURES

A new reimbursement policy for the utilization of quinolones was introduced in Alberta (Canada), and consisted of restricting the use of quinolones to defined subgroups of patients with common infections including urinary tract infection (UTI), upper respiratory infection (URTI), acute exacerbation of chronic bronchitis (AECB) and community acquired pneumonia. GPs were enrolled in the programme on a voluntary basis. The impact of this policy was evaluated in 2005 using time series analysis.³⁸⁰ The study observed no significant change in the monthly rates of all quinolone use (in prescriptions per 1000 index visits: -3.5%, 95% CI -5.5-1.4) following implementation of the programme. However a significant change in the rate of quinolone prescriptions per 1000 index visits for UTI (-33.6; 95% CI -23.8--43.4) and URTI (-16.1; 95% CI -11.6--20.6) was observed. Prescriptions of quinolone

were also significantly more consistent with the formulary guidelines after the implementation of the intervention compared to before (58.5% vs. 42.5%, $p=0.002$) but no change in hospitalisations, mortality or use of physicians services after implementation of the programme was observed.³⁸⁰

TRAINING IN COMMUNICATION SKILLS

In 2009, a RCT conducted in the Netherlands concluded that GPs trained in enhanced communication skills prescribed antibiotics to 27% of patients compared with 54% in the no training group ($p<0.01$).³⁷² A 3.5 years follow-up study of this RCT highlighted that patients who saw a family physician trained in enhanced communication skills were prescribed significantly fewer antibiotics during episodes of RTI in the subsequent 3.5 years (26.3% of all episodes in the intervention group compared to 39.1% in the group without intervention, $p=0.02$).³⁷¹

DELAYED PRESCRIPTIONS

Delayed antibiotic prescription, i.e. advice to delay the filling of an antibiotic prescription by at least 48 hours, was evaluated in a systematic review and meta-analysis.³⁴³ Authors estimated the effect of advising a delayed antibiotic prescriptions on clinical outcomes, antibiotic use, and patient satisfaction in RTIs.^{343, 338, 336} Delayed antibiotics resulted in a large and significant 96% reduction in antibiotic use compared to immediate antibiotics prescription (OR 0.04, 95% CI 0.03-0.05). Delayed antibiotic was however more likely to result in reported antibiotic use than no antibiotics prescribed (OR 2.55, 95% CI 1.59-4.08). There was no difference in patient satisfaction between delayed antibiotics and immediate antibiotics (OR 0.65, 95% CI 0.39-1.10).³⁴³

ANTIBIOTIC PRESCRIPTION FEEDBACK AND AUDIT

A RCT that included the 2 814 top antibiotic prescribers of Switzerland in primary care concluded no significant impact of feedback on rate of antibiotic prescriptions.³⁶² Another RCT in England included 1 581 GPs and concluded that the rate of antibiotic items dispensed per 1000 population was significantly lower in the feedback intervention group (126.98, 95% CI 125.7-128.3) than in the control group (131.3, 95% CI 130.3-132.2). Authors also



estimated that the feedback intervention created a £92 356 saving in direct prescribing costs for the public sector.³⁶³

A systematic review also concluded that no or only small changes in prescribing were observed with the use of audit and feedback alone.³⁴⁸

QUALITY INDICATORS OF ANTIBIOTIC USE

As is discussed in section 4.1.1.4, the European Surveillance of Antimicrobial Use (ESAC) project published in 2007 a set of 12 valid quality indicators for outpatient antibiotic use in Europe.¹⁰⁸ In an evaluation it was concluded that the utilisation of the ESAC indicators resulted in improved antibiotic prescribing in several European countries between 2004 and 2009, but that the impact of the initiative on the prudent use of antibiotics was not evaluated.³⁸³

COMBINATION OF INTERVENTIONS AT AMBULATORY LEVEL

A multifaceted behavioural change intervention was implemented in Utrecht (the Netherlands) and consisted in group education meeting, communication skills training, monitoring and feedback on prescribing rates, education material for patients, GPs and pharmacists (2 hour group education session).³⁶⁸ A RCT evaluated the impact of that intervention on antibiotic prescription rate and on satisfaction of the patients between 2000 and 2001, focused on the RTIs. A number of 89 practitioners completed the study. At baseline, prescription rates for antibiotics for RTIs did not differ between intervention and control group (27% vs. 29%, respectively). After nine months, the prescription rates in the intervention group fell to 23% whereas the control group rose to 37%; after 15 months, the number of antibiotic prescriptions in the intervention group was still lower than in the period before the intervention. The intervention did not change patients' degree of satisfaction.³⁶⁸

In 2005, a systematic review noted that multi-faceted interventions combining physician, patient and public education in a variety of venues and formats were the most successful in reducing antibiotic prescribing for inappropriate indications.³⁴⁸

A multifaceted intervention to promote the prescription of recommended first-line antibiotic for suspected UTI has been developed in Ireland between 2013 and 2014 among 71 GPs.³⁶⁰ The interventions included 4 main steps: 1) All GPs participated to a 'coding workshop' during which the study was explained and the importance of consultation coding for the audit reports, 2) Arm A received info on national guidelines for antibiotic use and result from the first audit report, Arm B received same info as Arm A, along with additional evidence to support delaying antibiotic prescriptions for suspected UTI. A reminder outlying guideline appeared when UTI code was used for both arm A and B. For Arm B, reminder also urged the physician to consider delayed prescription. The control group (Arm A) only received a workshop focused on coding practices, 3) a multimedia application was introduced (e.g. game for children) for intervention arms only. After the 6-month intervention period, control practices received all of the intervention materials, as well as their respective audit reports, and 4) a follow-up period of 5-month of passive data collection was performed. An absolute increase of 20% of antibiotic prescribing according to guidelines for practices was observed in the intervention arms, and patients attending an intervention practice were twice likely to receive a prescription for a first-line antimicrobial for their UTI compared to those in the control group. Improvements in guideline-based prescribing were sustained at 5 months after the intervention.³⁶⁰

In 2012, Van der Velden et al., 2012 also confirmed that multifaceted interventions comprising at least educational material for physicians were most frequently effective.³⁹⁰

A RCT in the Netherlands investigated the effect of communication training, electronic decision support tool and feedback on the RTI-related antibiotic prescriptions rate.³⁶⁹ Family physicians were selected among an extensive network of pharmacotherapy audit meeting groups (PTAM, series of regular meetings between GPs and pharmacists in the same area during which information and views about pharmacotherapy are exchanged). The interventions were: 1) family physicians communication skills training (and on delayed prescription), 2) implementation of antibiotic prescribing agreements in family physicians electronic prescription system, 3) feedback (using figures) for family physicians. The number of prescriptions decreased in all intervention PTAM groups after the multifaceted intervention, and for



patients of 12 years and older, the drop in the number of antibiotic prescription was significantly larger in the intervention group (-27.8 per 1000 patients) than in the control group (-7.2 per 1000 patients, $p < 0.05$). No significant effect of the multifaceted intervention was observed on children <12 years.³⁶⁹

6.1.2.5 Interventions targeting both hospital and ambulatory level

EDUCATIONAL ACTIVITIES FOR PRESCRIBERS AND PATIENTS

In 2014, a systematic review evaluated educational interventions aimed at improving antibiotic prescribing and dispensing practice in primary-care and hospital settings.³⁵¹ Educational interventions included any attempt to persuade physicians to modify their practice by communicating clinical information strategies and by communication skills training. The review included 78 studies (47 in primary care and 31 in hospital settings). The study reported improvement in adherence to guidelines and decrease of total antibiotics prescribed after education interventions, respectively, in 46% and 41% of all reviewed studies, changes in behaviour related to antibiotic-prescribing and improvement in quality of pharmacy practice, respectively in four and one studies. The majority of published studies about educational interventions described that active and multifaceted interventions are more effective strategies, and that respiratory disorders were the diseases targeted by most studies (mainly in primary care).³⁵¹

TOOLKIT FOR IMPLEMENTATION OF ANTIMICROBIAL STEWARDSHIP POLICY

In UK in 2011, two antimicrobial stewardship guidelines were introduced, one for hospitals, 'Start smart then focus',³⁹¹ and one for primary care, TARGET (Target Antibiotics Responsibly, Guidance, Education and Tools).ⁿⁿⁿ The 'Start Smart Then Focus' toolkit provides an outline of evidence-based antimicrobial stewardship in the secondary healthcare setting.^{ooo} The TARGET toolkit is designed to be used by the whole primary care team within the GP practice or out-of-hours setting. The toolkit included different resources (training resources, self-assessment checklist antimicrobial stewardship, etc.) that can be used flexibly, either as standalone materials or as part of an integrated package.³⁹² In 2016, the dental sector AMS toolkit^{ppp} for primary care was also launched in UK. As part of the roll out, different associations ran a joint social media campaign through a 'Thunderclap' providing a targeted pledge statement in which users gave permission to be broadcast via their social media accounts. The toolkit included resources (e.g. patient information leaflet), guidance, education and training tools, and audit tools. User feedback is currently under process.³⁹²

In the Netherlands in 2006, the Dutch Working Party on Antibiotic (SWAB) proposed an electronic national guide for the antibiotic treatment and prophylaxis of common infectious diseases in hospitals (SWAB-ID).^{qqq} Every hospital in the Netherlands was offered the opportunity to adapt this version to local setting and resources and distribute it through an independent website. A study reports that by the end of 2012, 40% of Dutch hospitals used a local customised version of SWAB-ID and 60% did not join the SWAB-ID initiative and continued to fully design their own guide.³⁹³ The study also investigated 50 antimicrobial guides and reported that the local

ⁿⁿⁿ TARGET Antibiotic toolkit, available at: <http://www.rcgp.org.uk/clinical-and-research/resources/toolkits/target-antibiotic-toolkit.aspx> (last access: 1 February 2019)

^{ooo} Antimicrobial stewardship: Start smart - then focus, available at: <https://www.gov.uk/government/publications/antimicrobial-stewardship-start-smart-then-focus> (last access: 1 February 2019)

^{ppp} Dental antimicrobial stewardship: toolkit, available at: <https://www.gov.uk/guidance/dental-antimicrobial-stewardship-toolkit> (last access: 1 February 2019)

^{qqq} SWAB-ID electronic national guide for hospitals available at: <http://www.ateams.nl/> (last access: 1 February 2019)



non-SWAB-ID based guidelines were significantly less comprehensive (64 vs. 90%, $p < 0.001$) and less followed national guidelines than SWAB-ID-based guides (46 vs. 70%, $p < 0.001$). Authors also reported that local SWAB-ID-using guides were more accurately kept up to date compared to non-SWAB-ID local guides.³⁹³

ECDC also developed a toolkit targeting the general public and the primary care prescribers, the EAAD toolkit, called 'What can you do to keep antibiotics working'.³⁹⁴ It offers key messages for each group of actors (hospital prescribers, hospital managers/administrators, infectious diseases specialists, infection, prevention and control and hospital epidemiologists, hospital pharmacists, nurses, microbiologists, emergency department, staff in intensive care units, staff in long-term care facilities) to 'keep antibiotics working'. This tool has not been evaluated yet.

NATIONAL ANTIMICROBIAL STEWARDSHIP REGISTRY

To measure the progress and impact of the national implementation of stewardship teams (A-teams) in every hospital, the Dutch Working Party on Antibiotic Policy (SWAB) is developing an antimicrobial stewardship registry.³⁹⁵ The registry reports on an annual basis both the quality of antibiotic use in hospitals in the Netherlands (based on defined quality indicators) and the stewardship activities employed by A-teams. In this manner, the register continuously provides data on the progress and impact of implementation of ASPs in Dutch hospitals. These data will be published in Neth-map^{rrr}, the annual national report which currently reports on use of antimicrobial agents and on antimicrobial resistance patterns.³⁹⁵

FINANCIAL INCENTIVES ACCORDING TO QUALITY INDICATORS

Since 2011, French hospitals are required to measure the compliance of the hospital ASP with recommended criteria regarding programme structure, organization, resources, and activities and this is translated into a composite

indicator that is publicly reported annually.³⁷⁹ These criteria include presence of an antibiotic advisor, computerized systems to assist with appropriate prescribing, local guidelines for antimicrobial prophylaxis and treatment, restricted antimicrobial initiation, education of prescribers, practice audit, surveillance of antibiotic usage, analysis of antibiotic resistance rates and feedback to prescribers. Since 2010, a financial penalty is applied if these indicators and others measuring compliance with infection control and quality-of-care standards are not disseminated by hospitals to their patients and the public. The result of this public reporting requirement is a commitment from hospital leaders and hospital employees to comply with ASP recommendations. Low values of the composite indicator have a negative impact on the hospital's reputation and accreditation results and will trigger an action from health authorities that, in turn, will urge hospital leaders to address and improve compliance.^{355, 396}

In 2015 in UK, antimicrobial prescribing and stewardship skills have been developed for prescribers and two incentive schemes were introduced to decrease antibacterial prescribing, i.e. the Quality Premium (QP) and the Commissioning for Quality and Innovation (CQUIN) framework. The QP^{sss} is intended to reward Clinical Commissioning groups (CCGs) for improvements in the quality of the services and the creation of new, improved patterns of care across various health provider types, focusing on reducing antibiotic prescribing. The National Health Service Business Services Authority provide quarterly data on antibiotic prescribing in the ambulatory sector, while Public Health England openly publishes QP indicator on 'Fingertips' data portal^{ttt}. Almost 2.7 million fewer antibiotics were dispensed in 2015-16 compared to 2014-15, following the introduction of the AMR QP. The median proportion of broad-spectrum antibiotic (co-amoxiclav, cephalosporins and quinolones) as a proportion of all antibiotics items reduced from 10.8% to 9.6%. Almost 17 600 fewer antibiotic were dispensed in 2016-17 compared to 2015-16.³⁹² The CQUIN framework supports improvements in the quality of services and the creation of new,

^{rrr} Neth-Map, available at: https://www.rivm.nl/Onderwerpen/I/ISIS_AR/Overzichten_van_de_gegevens/Nethmap (last access: 1 February 2019)

^{sss} Quality premium guide 16/17 available at: <https://www.england.nhs.uk/resources/resources-for-ccgs/ccg-out-tool/ccq-ois/qual-prem/> (last access: 1 February 2019)

^{ttt} AMR local indicators available at: <https://fingertips.phe.org.uk/profile/amr-local-indicators> (last access: 29 January 2019)



improved patterns of care across various health provider types, focusing on reducing antibiotic prescriptions in acute Trusts. The aim of this CQUIN was to reduce antibiotic use, to encourage a focus on AMR and to ensure that prescriptions are reviewed within 72 hours of commencing antibiotic. CQUINs are the main mechanism by which the NHS encourages hospitals to focus on the quality of care delivered by making a proportion of income conditional on achieving specific quality measures. All data submitted by hospitals are also available on the 'Fingertips' data portal as part of the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR).³⁹² In 2018, the impact of this initiative was evaluated throughout UK hospitals.³⁹⁷ Results indicate that CQUIN initiative was associated with a reduction in antibiotic use, and the annual trend for increased antibiotic use reversed in 2016-2017. In 2014-2015, year-on-year changes were +3.7%, +9.4% and +5.8% for total antibiotics, piperacillin/tazobactam and carbapenems, respectively, and +0.1%, -4.8% and -8.0% in 2016/2017.³⁹⁷

DISPENSING THE EXACT NUMBERS OF TABLETS

Dispensing the exact numbers of antibiotic tablets in pharmacies through fractionation is implemented in the UK, the Netherlands, US, Japan, Israel and the Czech Republic.^{217, 230, 238} A study demonstrated that in countries where antibiotics were dispensed per package size, respondents had a four times higher risk of having leftover antibiotics and a five times higher risk of saving them and giving them to someone else.²³⁰

A European study confirmed that at the country level, the exact dispensation of prescribed tablet quantities by pharmacies was independently associated with a lower likelihood of self-medication (OR 0.51, 95% CI 0.27-0.98).²³⁴ Finally, a RCT in France demonstrated that dispensing the exact number of pills reduced by 10% the number of pills supplied and that per-unit dispensing improved adherence to antibiotic treatment (marginal effect 0.21, 95% CI 0.14-0.28).³⁹⁸

COMBINATION OF INTERVENTIONS TARGETING BOTH HOSPITAL AND AMBULATORY SECTOR

In Scotland, a national stewardship initiative took place between 2006 and 2011. The strategy was built around four axes: 1) restriction use of cephalosporins, co-amoxiclav, clindamycin, fluoroquinolones and macrolides antibiotics, 2) hand hygiene campaign, 3) hospital environment inspection, and 4) MRSA admission screening. In a time-series analysis that included 1 289 929 hospital admissions and 455 508 adults registered in primary care, Lawes et al., 2015 estimated that during the Scottish antibiotic stewardship intervention, the use of cephalosporins, co-amoxiclav, clindamycin, fluoroquinolones and macrolides antibiotics fell by 47% in hospitals and 27% in the ambulatory sector and that MRSA prevalence density was reduced by 50% in hospitals and by 47% in the ambulatory sector.³⁷⁶

6.1.2.6 Interventions targeting the general public, patients

WORLD ANTIBIOTIC AWARENESS WEEK (WAAW) AND EUROPEAN ANTIBIOTIC AWARENESS DAY (EAAD)

Each year in November, the WHO initiates the World Antibiotic Awareness Week (WAAW). The aim of this week is to increase awareness of global antibiotic resistance and to encourage best practices among the general public, health workers and policy-makers to avoid the further emergence and spread of antibiotic resistance. On this occasion, WHO proposes different campaign material and tools.^{uuu} As part of the WAAW, since 2008 ECDC initiates the European Antibiotic Awareness Day (EAAD) on the 18th of November on which most of the European countries participate.^{vvv} In UK in 2016, children, families, scouting groups, universities, healthcare students and community pharmacist were engaged to celebrate WAAW and EAAS. More than 367 organisations registered planned activities and participation

^{uuu} WHO tools; available at: <http://www.who.int/campaigns/world-antibiotic-awareness-week/en/> (last access: 29 January 2019)

^{vvv} A summary of national initiatives; available at: <https://antibiotic.ecdc.europa.eu/fr/campagnes-en-europe> (last access: 29 January 2019)



with Google analytics revealed that there were 18 404 views of the antibiotic awareness resources .gob page during the WAAW.³⁹²

MASS INFORMATION CAMPAIGNS IN OTHER COUNTRIES

In Poland, a campaign educational material aimed at the general public was undertaken in five waves between 2009 and 2011. A 2017 study demonstrated that 48% participants who had come across information about antibiotics during the campaign declared that the information resulted in a change in their attitude towards antibiotic use.³⁹⁹

In Sweden, the Swedish strategic programme against antibiotic resistance (STRAMA^{www}) was created in 1994 to improve the prudent use of antibiotics and contain antibiotic resistance. Activities are implemented at both national and local level, such as monitoring of antibiotic prescribing and sales, monitoring of antibiotic resistance, feedback of these data to prescribers, development of educational outreach for new national guidelines, participation in various types of national and local studies, communication with media and participation in international networks and collaborations. Specific activities at the local level include educational activities for health-care personnel, staff at preschools, nursing homes, and parents.⁴⁰⁰ In 2008, a study showed the effectiveness of the STRAMA programme on the reduction of antibiotic use. Between 1995 and 2004, antibiotic use for outpatients decreased from 15.7 to 12.6 DDD per 1000 inhabitants per day and from 536 to 410 prescriptions per 1000 inhabitants per year.³⁸² The last national report on Swedish antimicrobial utilisation and resistance in human medicine noted that antibiotic use is continuing to decrease in Sweden. Indeed, the total antibiotic sale in humans decreased by 1.9% in 2017 compared with 2016 (from 12.5 to 12.3 DDDs per 1000 inhabitants and day).⁴⁰¹

^{www} STRAMA program; available at: <http://strama.se/about-strama?lang=en> (last access: 29 January 2019)

^{xxx} « Les antibiotiques c'est pas automatique » campaign videos available at: <https://www.youtube.com/watch?v=dXNon2bCWxo> and

6.1.2.7 The experience of France

In the early 2000s, France faced growing problems with multidrug-resistant pneumococci, and was identified as the country with the highest antibiotic use in Europe and one of the highest antimicrobial users worldwide.⁴⁰² Therefore, the first national antibiotic plan (2001-2005) was launched to preserve antibiotic efficacy. The French National Health Insurance initiated a long-term nationwide campaign to reduce antibiotic overuse and to control the dissemination of resistant bacteria in the ambulatory sector.³⁷⁷ The objective of this campaign was to decrease the total antibiotic use in the ambulatory sector by 25 %, targeting mainly viral respiratory infections in young children. The national programme named 'Keep Antibiotics Working', was launched in 2001, targeting both the general public and health care professionals to encourage the surveillance of antibiotic use and resistance and to promote a better-targeted antibiotic use.³⁷⁷ From 2002, a public service campaign entitled 'Les antibiotiques c'est pas automatique' ('Antibiotics are not automatic')^{xxx} was launched each winter with the primary goal of decreasing prescriptions. The general public campaign appeared in national media outlets, consisting of prime-time television and radio ads, newspaper ads.³⁷⁷

An educational campaign was also initiated for healthcare workers (GPs, paediatricians in community practice, and day-care workers), using a face-to-face education and guideline dissemination. In addition to providing information on appropriate antibiotic use, the campaign promoted the use of rapid tests to diagnose group A streptococci (RTAS) tonsillitis. Physicians were invited to county-level trainings on how to use RTAS and optimize antibiotic use. They were also visited by a physician of the National Health Insurance for face-to-face peer education sessions. Free tests were provided to physicians who attended the training. Antibiotic guidelines were sent to targeted practitioners and distributed during training and visits. Day-care workers were also trained to not systematically require antibiotic treatment as a condition for day-care attendance of children with viral

<https://www.youtube.com/watch?v=ydq6zY4yhEw> (last access: 29 January 2019)

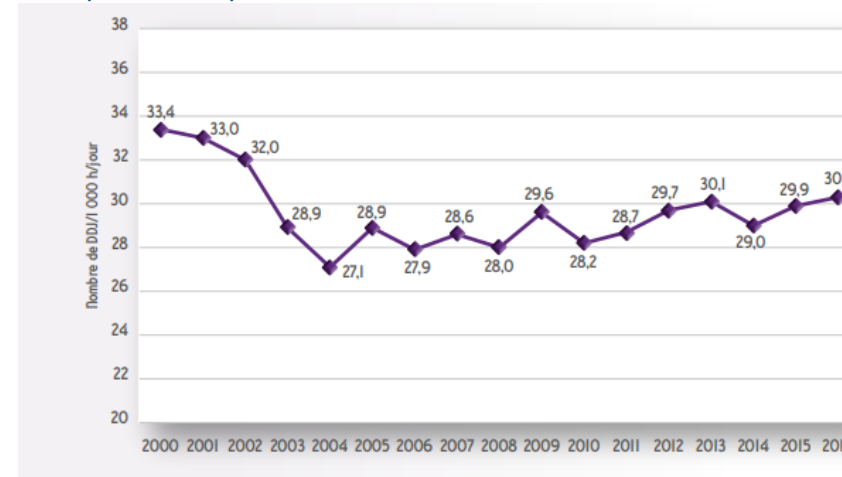


respiratory infection as well as to relay the message of optimal use of antibiotics to parents.³⁷⁷

The French Ministry of Health has also required hospital antimicrobial stewardship programmes (ASP) since 2002 and the reporting of compliance with specific programme performance since 2007. As already mentioned in section 6.1.2.5, French hospitals are also required to measure the compliance of the hospital ASP with recommended criteria regarding programme structure, organization, resources, and activities from a composite indicator that is publicly reported annually,³⁷⁹ and since 2010, there has also been a financial penalty if these indicators and others measuring compliance with infection control and quality-of-care standards are not disseminated by hospitals to their patients and the public.^{355, 396}

After the nationwide campaign initiated in the early 2000s, the total number of antibiotic prescriptions per 1000 inhabitants changed by -26.5%, 95% CI -33.5 to -19.6% over 5 years and the decline occurred in all 22 regions of France and affected all antibiotic therapeutic classes except quinolones. The initial objective of the 'Keep Antibiotics Working' programme to reduce antibiotic use in the ambulatory sector by 25% was reached within 5 years.³⁷⁷ However, the effect of this national campaign has quickly faded, and despite two other antibiotic national plans initiated in 2007 and 2011, antibiotic use increased again from 2010 onwards in France. Increases of antibiotic use are mainly observed in the cities, where antibiotic use increased by 5.6% between 2011 and 2016, indicating a growth of 1.3% between 2015 and 2016 (Figure 19).

Figure 19 – Evolution of antibiotic use in DDD/1000 inhabitants/day in cities, 2000-2016, France

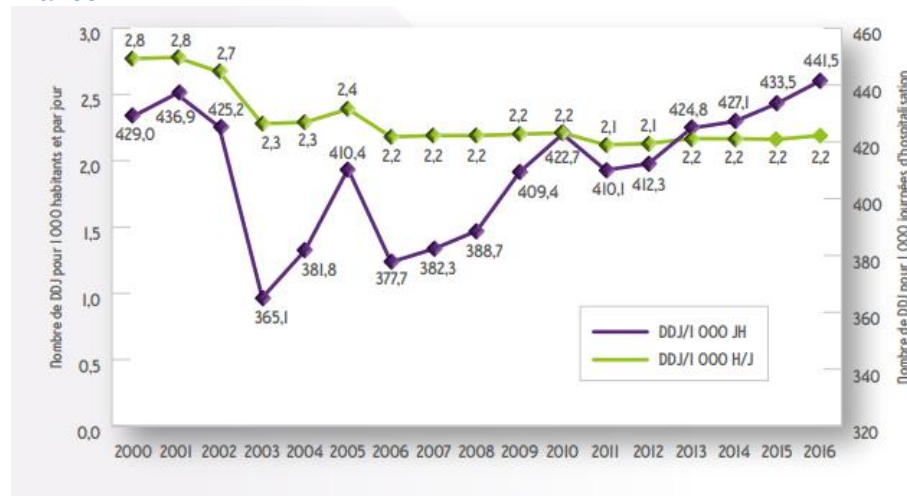


Source: Agence nationale de sécurité du médicament et des produits de santé⁴⁰³

At the hospital level, the use decreased significantly between 2000 and 2016. However, when the use is expressed in numbers of DDD by number of days of hospitalization (and no longer by population), the use tends to increase. However, this second indicator, which takes into account the hospital activity, is difficult to interpret over a long period. Indeed, the evolution in patient management leads to a reduction in the overall number of days of hospitalization, but not necessarily to a lower use of antibiotics (Figure 20).



Figure 20 – Evolution of antibiotic hospital use in DDD/1000 inhabitants per day (left) and DDD/1000 hospitalization days (right), 2000-2016, France



Source: Agence nationale de sécurité du médicament et des produits de santé ⁴⁰³

In the face of these worrying trends, a call for a more determined and lasting mobilisation against antibiotic use and resistance was launched in France in November 2016.⁴⁰⁴ A new alert plan was developed and four axes of improvement have been proposed by a Task Force in 2015: 1) adopt a national strategy in favour of antimicrobial resistance research and development of innovative products to combat the bacterial resistance to antibiotics, 2) propose a set of indicators to measure, observe and monitor antibiotic resistance and cost in time, 3) improve the good use by financing support structures for the prescriptions of antibiotics, making available educational tools for prescribers, strengthening individual and collective professional responsibility and, 4) enhance public awareness of antimicrobial resistance through long-term local and national actions.⁴⁰⁵ The roadmap for controlling the antimicrobial resistance of the Interministerial Committee for Health,⁴⁰⁶ as well as the 'prevention and control of antimicrobial resistance' component of the National Programme for the

Prevention of Health-Associated Infections set also the framework, objectives and actions to be led in France in the following years.⁴⁰⁷

Key messages

- We retrieved a number of systematic reviews on specific interventions targeting the prudent use of antibiotics. However, the evidence was difficult to extract as a variety of interventions, varying by country or even by hospital, were evaluated using different methodologies, and different outcomes.
- Antibiotic stewardship programs are mainly multifaceted, i.e. they include several types of interventions, have different target populations and objectives. This limits the ability to derive clear conclusions on their effectiveness.

At the hospital level, ten interventions are described:

- Antimicrobial management team had a significant impact on reducing antibiotic use and costs in France and the Netherlands.
- Specific stewardship interventions, such as restricting the list of antibiotics, promotion of rapid parenteral to oral switch, promotion of de-escalation of therapy, point-of-care testing (i.e. CRP and PCT) and the use of computer-assisted decision tools and quality indicators showed a significant effect on at least one outcome, such as reducing antibiotic use, duration of antibiotic treatment, hospital length of stay and costs. Some of these interventions also reduced the mortality rate.
- Combination of several interventions enhanced the effectiveness of the intervention and increased compliance with antibiotic policies. Persuasive interventions coupled with restrictive measures also reduced the length of stay. Persuasive measures that included feedback were more effective than those that did not.



At the ambulatory level, eight interventions are described:

- Point-of-care testing, restricting the type of antibiotics using financial measures, training GPs in communication skills and delayed prescriptions, all reduced antibiotic prescription and use, but did not change the number of consultations and hospitalisations. Educational activities for ambulatory prescribers and patients showed a limited impact on prudent use of antibiotic, and antibiotic prescription feedback and audit showed contradictory results.
- Combination of interventions showed positive results on the prudent use of antibiotics but the magnitude of the impact depends on the type of intervention included in the program.

At both hospital and ambulatory sector, six interventions are described:

- Educational activities for prescribers and patient showed positive impact on adherence to antibiotic guidelines, in particular when they are combined with other interventions. Financial incentives according to quality indicators decreased significantly the antibiotic use in UK. Dispensing the exact numbers of tablets was associated with a lower likelihood of self-medication and a better adherence to antibiotic treatment.
- Combination of interventions targeting both hospital and ambulatory sector, and more particularly combination of 1) restriction use of cephalosporins, co-amoxiclav, clindamycin, fluoroquinolones and macrolides antibiotics, 2) hand hygiene campaign, 3) hospital environment inspection, and 4) MRSA admission screening, showed a positive impact on antibiotic use and MRSA prevalence in hospitals and in the community.

In nursing homes:

- Overall, effects of the interventions in nursing homes were mixed and modest.

Overall:

- Mass information campaigns seems to significantly decrease antibiotic use in several countries but in France the effect of campaigns quickly faded.

6.2 Interventions to promote the prudent use of antibiotics in the veterinary sector

6.2.1 Introduction

In the following sections we provide an overview of the nation-wide interventions to promote the prudent use of antibiotics in the veterinary sector. We did not perform a systematic literature search, since interventions are mostly documented in grey literature and in regulations. Hence we performed mainly web based desk research (from January until July 2018). In addition, we asked experts in the field to complement our inventory. An overview of the interventions in Belgium and Europe is provided in Table 45. Although many organisations involved in animal health care or animal husbandry, such as animal health care Flanders ('Dierengezondheidszorg Vlaanderen'), or professional organisations for farmers (Association régionale de santé et d'identification animale (ARSIA), Boerenbond, Algemeen Boerensyndicaat and the Fédération Wallonne de l'Agriculture, the latter three united in Agrofront), have also taken small scale or punctual initiatives (e.g. conferences, a biosecurity^{yyy} award) to promote the prudent use of antibiotics, the One Health approach and alternatives to antibiotic use (e.g. biosecurity measures), these are not included in this section as it focuses on initiatives taken at the national level.

^{yyy} Biosecurity refers to all measures taken to prevent both the introduction and the spread of infectious agents on the farm.⁴⁰⁸



As the literature review revealed some interesting scenarios developed in other European countries, the Netherlands and Denmark, these models are described in section 6.2.5.

Table 45 – Interventions for prudent antibiotic prescription and veterinary use

Intervention	Date	Evaluation study
<i>Belgian</i>		
Policy measures		
Covenant zinc oxidez and medicated feed	30 January 2013	None
Tax on veterinary antibiotics	1 June 2014	None
Covenant on the decrease of antibiotic use in animals	1 June 2016	None
Legal conditions for the use of certain critically important antimicrobials (CIAs – see Box 21)	RD 21 July 2016	None
Obligatory registration of antibiotic use in SANITEL-MED	27 February 2017	None
Guidelines		
Guidelines for prudent antibiotic use in animals – e-vademecum		Sarrazin et al., 2017 ²⁶³
Sensitisation campaigns		
AMCRA roadshows		None
AMCRA national sensitization campaign by means of TV spots and posters		None
Academic initiatives		
AB check web-tool		None
Biocheck.UGent scoring system		Gelaude et al., 2014 ⁴⁰⁸
Biosecurity audit		Postma et al., 2017 ⁴⁰⁹
<i>European</i>		
Policy measures		
EU ban on antibiotics as growth promotor	2006	Diana et al., 2017 ⁴¹⁰

AB: Antibiotic; EU: European Union; RD: Royal Decree.



6.2.2 Nation-wide interventions to promote prudent antibiotic use

6.2.2.1 Policy measures

The covenant on the decrease of antibiotic use in animals: from autoregulation to co-regulation

Since its foundation in 2012, AMCRA has done a large effort of stimulating autoregulation in different animal sectors in order to reduce antibiotic use in animals (see also section 3.4.3). In 2016, three AMCRA 2020 goals (see Box 12) were ratified by an agreement between the Belgian Federal Government and the stakeholders regarding the decrease in antibiotic use in animals.⁸⁶ Apart from the strategic goals, also a number of operational goals were agreed upon (see Table 46).

Table 46 – Operational goals and their status

Operational goals	Status
1. Further development and maintenance of SANITEL-MED by the government (FAGG)	Ongoing
2. Obligatory registration in SANITEL-MED by veterinarians of every prescription, provision and administration of antibiotics for pigs, roast chickens, laying hens and veal calves in a first step and gradually the other sectors too	Ongoing
3. Feedback and benchmarking of farmers and veterinarians through the analysis of the SANITEL-MED data	Ongoing
4. The development and publication (on the AMCRA website) of a generic business health plan and action plan for all animal sectors	Published on the AMCRA website
5. The development of target values and alarm values per sector and age category. Follow-up and correcting measures when exceeding alarm values are enforced by auto-regulation. In addition benchmark values will be developed for veterinarians. Initially the label schemes will organise the follow-up (through benchmarking of farmers), but from 2021 onwards FAVV – AFSCA and FAGG – AFMPS will take over. They will also enforce correcting measures when vets exceed the alarm values	Ongoing
6. The pharmaceutical industry has been asked to adapt package leaflets of antibiotics authorised in Belgium in such a way that they do no longer contain preventive indications, except for specific cases	Done. Quasi no preventive indications left in package leaflets.
7. Stakeholders and government are setting-up an awareness campaign to inform all actors involved about the necessity of decreasing/changing antibiotic use and the availability of alternatives	Ongoing (AMCRA)
8. The responsible governmental bodies increasingly supervise the correct application of the existing legislation regarding antibiotic use and registration in SANITEL-MED	Ongoing (inspection services FAVV – AFSCA and FAGG – AFMPS)
9. Antibiotics resistance is monitored by the government and results are made publicly available	Ongoing (Sciensano, coordinated by EFSA and FAVV)



Several of these goals depend on the analysis of the SANITEL-MED data (see section 4.2.2.1). Although the autoregulation efforts seem quite fruitful (based on BelVet-Sac and SANITEL-MED data), the government has taken additional measures to reach the 2020 goals and execute the operational goals mentioned in Table 46. These additional measures are introduced by the Royal Decree of 21 July 2016 and consist mainly of the obligatory registration of antibiotic use in SANITEL-MED and the formulation of conditions for the use of critically important antimicrobials.⁵⁷

Obligatory registration of antibiotic use in SANITEL-MED

As has been described above, all prescribed, supplied and administered antibiotics for veterinary use are registered in SANITEL-MED (see section 4.2.2.1). The legislation for mandatory registration took effect on 27 February 2017. Veterinarians must register the use of antibiotics in production animals in the SANITEL-MED application. Registration is mandatory for poultry (laying hens and broilers), pigs and veal calves.⁵⁷

Legal conditions for the use of certain critically important antimicrobials

From August 2018 onwards, certain critically important antimicrobials (CIAs, see Box 21), more precisely third and fourth generation cephalosporins and first, second and third generation fluoroquinolones, can only be prescribed and used under strict conditions:⁵⁷

- a clinical examination takes place on the spot by the treating veterinarian;
- a bacterial cause of the infection is confirmed;
- appropriate samples are taken or a post-mortem requested;
- the bacterial strain involved is confirmed based on the samples taken;
- a standardised laboratory antimicrobial sensitivity test is performed, including seven non-critical antimicrobials of at least five different classes as well as the CIAs;
- and the test result indicates that it is the only effective antibiotic.

Samples must be taken at the time of initiating therapy, sensitivity testing must be performed and the treatment must be re-assessed based on the available results of the sensitivity testing.

Note that these conditions are not obligatory in two exceptional situations: in case of urgency or the impossibility to take a sample. A veterinarian may, under his own responsibility and after clinical examination, administer a CIA if he has reasons to expect that this CIA is the only therapy capable of saving the life of the animal or preventing irreversible damage.

From the consultation of stakeholders we learnt that in practice the conditions imposed by the Royal Decree imply that quasi no CIAs are used anymore. Both the BelVet-Sac results (2016 and 2017) as well as the SANITEL-MED data (available since 27/02/2017) confirm the strong decrease in the use of CIA's, especially the cephalosporines of the 3th and 4th generation and the fluoroquinolones.^{128, 131, 133}

Tax on veterinary antimicrobials

Since June 2014 marketing authorisation holders pay a tax on veterinary antimicrobial sales based on the volume of sales on the Belgian market. The tax is from April 2018 onwards € 3.06 per kg of antibiotic active substance sold and € 4.59 per kg of certain critically important antimicrobials (i.e. fluoroquinolones, cephalosporins and macrolides). The minimal contribution per package is € 0.01.^{411, 412}

The total returns generated by this tax range between 450 000 to 500 000 euro/year and serve the funding of all AMR and prudent antibiotic use initiatives supported and financed by FAGG – AFMPS and relevant data collection and analysis (e.g. taxes are used to finance AMCRA, BelVet-Sac, the SANITEL-MED application). It acts less as a financial disincentive to the use of antibiotics. (FAGG – AFMPS, *personal communication*)

The impact of this measure on the antibiotic use is unclear. Presumably, taxes are too low to influence the use of antibiotics or to stimulate alternative treatments and/or prevention measures.



Covenant on zinc oxide² and medicated feed

In 2013, a covenant has been signed between FAVV – AFSCA and the Belgian Federation representing feed producers (BFA) in order to improve the conditions in which medicated feed is produced, i.e. preventing cross contamination of medicated feed with non-medicated feed.⁴¹³ More specifically feed producers engaged to add the premix to the feed in a later stage of the production process, i.e. when delivered to the farm, to minimise the contamination risk. In addition, control mechanisms were sharpened and BFA promised to sensitize the sector about medicated feed and antibiotic use. A yearly survey among the 61 feed producers will enable BFA and FAVV – AFSCA to observe the compliance with the covenant. The covenant is not compulsory, hence feed producers are not legally obliged to comply.⁴¹⁴

The impact of this measure is unclear.

6.2.2.2 Guidelines

Guidelines for prudent antibiotic use – e-vademecum

From 2013 onwards AMCRA has developed formularies, which contain guidelines for practising veterinarians on therapeutic indications per animal species (pigs, cattle, horses, dogs, cats and poultry) and per disease. For each pathology antimicrobial active substances are classified in first, second and third choice. They are given a colour label reflecting their importance for human and animal health based on the prioritisation given to these by WHO and OIE, respectively.^{148, 415} Yet, priority was given to human health. Each **colour code** implies different terms of use:¹³¹

- The group of **yellow** products contains the antibacterial classes with the lowest importance for human medicine in terms of resistance selection and transfer and therefore no additional restrictions, on top of the legal requirements, are suggested for their use. This group contains the majority of the penicillins, the sulphonamides (and diaminopyrimidines), the cephalosporins of the first generation and the phenicols.
- The group of **orange** products are of higher importance for human medicine and should therefore be used restrictively; only after good diagnostics allowing to target the therapy. This group comprises the highest amount of different molecules including all available macrolides,

the polymyxins, the aminoglycosides, the tetracyclines and the aminopenicillins.

- The **red** group of products are the products of **highest importance for human medicine** and therefore their use should be avoided in veterinary medicine as much as possible. AMCRA advises to use these molecules only under very strict regulations. This group contains the 3rd and 4th generation cephalosporins and the fluoroquinolones.

Since 2016, the formularies are free of charge available on the website www.e-vademecum.be.⁴¹⁶

To the best of our knowledge the use of these formularies has not been evaluated in Belgium, except for companion animals. In a recent prospective Belgian study on the prescription habits in fourteen Flemish first-line, small animal practices during first consultations of cats and dogs, the impact of the guideline for prudent antibiotic use in cats and dogs has been explored. The number of consultations of cats and dogs complying with the antimicrobial use guidelines increased with respectively 13 and 10 percent when comparing prescription behaviour 20 days after the implementation of the guidelines to one month before implementation. However, at the same time an increase in the prescription of third-choice antibiotics and highest priority CIA's was noticed with respectively 8% and 12% in cats and both 5% in dogs. The authors did not find an explanation for this unexpected finding.²⁶³

6.2.2.3 Sensitization initiatives

AMCRA road shows

One of the sensitization activities organised by AMCRA (in collaboration with FAVV – AFSCA) comprises road shows, during which veterinarians and farmers are informed about the prudent use of antibiotics and antibiotic resistance. In total 21 sessions were organised (9 for veterinarians and 12 for farmers) which were attended by 930 veterinarians and 1 180 farmers.⁸⁰ The Dutch Speaking Supreme Council of the Order of Veterinarians (NGROD) assigned the attending veterinarians a continuing professional development credit.⁸⁰

On demand AMCRA also visits local reunions of veterinarians or farmers to present their goals and activities, and sensitize about antibiotic use.



AMCRA TV spots and posters

TV spots on the prudent use of antibiotics in veal calves, dairy cattle, poultry, pigs and companion animals and antibiotic resistance are regularly shown at channels specialised in topics relative to country life (e.g. country television channel ('Plattelands TV')) and they are also available on the AMCRA website (in Dutch and French).

About 10 000 stable-proof sector-specific posters with prudent antibiotic use guidance were developed by AMCRA and financed by Pharma.be. They have been distributed directly to farmers via agricultural fairs and veterinarians.⁸⁰ These posters are available in Dutch and French at the AMCRA website. The posters and TV spots are about the same animal species.

To the best of our knowledge, the impact of these sensitization interventions has not been evaluated so far.

6.2.2.4 Autoregulatory initiatives

Since October 2016, feed medicated with antibiotics, zinc oxide^z and/or anthelmintics (medication against worms) can only be prescribed through electronic prescription by the farm veterinarian. This initiative has been taken by the Belgian Feed Association (BFA), who provided an application for that specific purpose.⁴¹⁷ There is currently no legislation supporting this initiative.

6.2.2.5 Academic initiatives

Antibiotic check web tool

The antibiotic check web tool, was a free web-based tool, developed for farmers to calculate their antibiotic use and compare their results with other farms. Currently the tool is no longer in use, because it has become superfluous with the development of the SANITEL-MED registration system.⁴¹⁸

Biocheck.UGent scoring system

At the Faculty of veterinary medicine at Ghent University a Biocheck scoring system has been developed to measure the biosecurity^{yy} on farms and quantify the relationship with technical performances (e.g. average daily

growth, total mortality, feed conversion) and antibiotic use. The tool is composed of all relevant components of biosecurity, both external (e.g. feed and water supply, removal of manure, entrance of visitors and personnel) and internal (e.g. disease management, cleaning and disinfection), resulting in a risk-based weighted score. The Biocheck.UGent scoring system and accompanying questionnaire can be filled in for free at www.Biocheck.UGent.be. The obtained biosecurity scores are provided immediately after completion of the questionnaire. The scores can be compared to national averages, allowing the farmer to benchmark with colleagues.⁴⁰⁸

The biocheck instrument was used in a pilot group of 15 broiler farms in Flanders. Preliminary results show a promising trend in the relationship between biosecurity and antibiotic use. There was an average reduction in antimicrobial use of 29% after optimisation of the biosecurity in the participating farms. Because of the small number of participating farms, and the limitation to broiler farms only, further research is needed to investigate whether biosecurity can have a large effect on antibiotic use.⁴⁰⁸

Biosecurity audit

The biosecurity audit was a research project running from 2010 until 2014 and initiated by the quality label Certus and the farmers' union 'Boerenbond'. The study aimed at evaluating the potential reduction in antibiotic use by promoting prudent usage combined with farm management optimization through the guidance of farmers or veterinary coaching.⁴⁰⁹ The intervention study was conducted on 61 Flemish pig herds and included three visits per herd. During an initial visit, information was gathered on herd management, biosecurity status, vaccination strategy, and antibiotic use. This information was translated in a herd-specific action plan which was discussed with the farmer and herd veterinarian during the second visit. During the third visit, the impact of the action plan was evaluated. A significant reduction in antibiotic use was reached with a decrease of 52% for the pigs from birth till slaughter and 32% for breeding animals.⁴⁰⁹ This also included an important reduction in the use of critically important antimicrobials. In addition increased biosecurity and decreased antibiotic use did not jeopardize production results. Hence, the researchers concluded that veterinary coaching or guided interventions as a team effort of farmer and herd



veterinarian are a promising method in the reduction of antibiotic use in pig production.⁴⁰⁹

6.2.3 European initiatives

6.2.3.1 EU ban on antibiotics as growth promotor

Added in low doses to the feed of farm animals, antibiotics are considered to improve the quality of the meat, more precisely a lower percentage of fat and a higher protein content. Other benefits of the use of antibiotic growth-promoters include control of zoonotic pathogens such as Salmonella, Campylobacter, Escherichia coli and enterococci.⁴¹⁹ However, since the use of any antibiotic is associated with the selection of resistance in pathogenic bacteria and since its use also imposes a selection pressure for bacteria that are resistant to antibiotics that may be used in clinical or veterinary practice, thus compromising the continued use of antimicrobial chemotherapy, the European Commission decided in 2006 to ban the marketing and use of antibiotics as growth promoters in feed. After the ban, antibiotics were only allowed to be added to animal feed for veterinary therapeutic purposes (e.g. treatment of sick animals).

An experimental study performed in Ireland evaluated the effect of removing antibiotics from the feed of weaner pigs and noted that this measure had minimal effects on health and welfare indicators (e.g. tail, ear and flank biting).⁴¹⁰

In Sweden the use of antimicrobial growth promoters was banned as early as 1986. In a paper assessing the Swedish ban it was concluded that although total antibiotic use increased in the 4 subsequent years, it decreased afterwards because of improved management.⁴²⁰ The authors conclude that under good production conditions it is possible to reach good and competitive production results for the rearing of poultry, calves, and pigs without the continuous use of antibiotics as growth promotor.

6.2.4 Concluding remarks

With the exception of the aforementioned study²⁶³ on the impact of guidelines on the prescription of antibiotics for companion animals,²⁶³ and the study on the impact of a herd-specific action plan with guidance for the

farmer and herd veterinarian,⁴⁰⁹ no effect measurements are available of the interventions described above. Hence, it is impossible to identify which initiatives can be recommended to be initiated and where appropriate prolonged and in which ones it is not useful to spend time and energy. Yet, a number of scientific publications on the relationship between on the one hand adequate biosecurity measures and farm management and on the other hand antibiotic use, show that the optimization of herd management, improvement of the biosecurity and guidance on prudent antibiotic use are promising routes of action to achieve the reduction of antibiotic use, without jeopardizing production results.^{254, 408, 409, 421-423}

6.2.5 Examples from abroad

The literature review revealed some interesting scenarios developed in other European countries, the Netherlands and Denmark; they are described in the following paragraphs.

6.2.5.1 The Dutch example

Dutch efforts to reduce veterinary antibiotic use

In 2005, it was reported that livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) was widely spread in the Dutch pig population. This discovery was followed by societal and political pressure to reduce antibiotic use in farm animals.²⁴⁵ As a response the Taskforce Antibiotic Resistance in Animal Husbandry was set up in 2008. It comprised representatives of all stakeholders in the animal production chain. Action plans per animal production sector were developed as part of a Memorandum of Understanding with the aim to control antibiotic resistance in livestock.²⁴⁵ No strict targets or regulations for antibiotic use were yet formulated, but still the action plans included detailed monitoring of antibiotic use at herd level, monitoring of antibacterial resistance, description of responsibilities of veterinarians and farmers in antibiotic prescribing and use, and the introduction of farm treatment plans and farm health plans.²⁴⁵

In 2009, extended-spectrum beta-lactamase producing bacteria (ESBLs) were found in Dutch poultry meat and a possible relationship with a human casualty was widely discussed in the Dutch media. The Government responded with the introduction of a compulsory 20% and 50% reduction



target in antibiotic use in farm animals in 2011 and 2013 respectively, with 2009 as reference year.²⁴⁵

In 2010, the independent Dutch Veterinary Medicines Authority ('Stichting Autoriteit Diergeneesmiddelen', SDa) was founded to monitor antibiotic use. This independent body has to collect reliable data on antibiotic prescription and use from all individual farms and veterinarians in the Netherlands. In addition, it has to set species specific benchmark indicators that differentiate between moderate, high and very high users and prescribers, so that high prescribers and users can be subjected to disciplinary sanctions.²⁴⁵

The Dutch Health Council ('Gezondheidsraad'), an independent scientific advisory body for the government and parliament, presented in 2011 recommendations to prevent further development and spread of antibiotics resistant bacteria in animal production.²⁴⁵ Examples of recommendations are:

- The exclusive use of newly developed antibiotics for humans;
- An immediate ban on preventive and systematic therapeutic group treatment in animals with the critically important 3rd and 4th generation cephalosporins and fluoroquinolones;
- A persevering prudent use of colistin and the phasing out of all preventive and systematic veterinary use of β -lactam antibiotics and aminoglycosides in animals.

The private quality assessment systems ('Integrale Keten Beheersing', IKB) translated these recommendations in specific regulations that restricted the use of 3rd and 4th generation cephalosporins and fluoroquinolones in farm animals. The government incorporated the private regulations into legislation and additionally banned all preventive use of antibiotics in animals.²⁴⁵

In addition to these measures the independent position of veterinarians had to be reinforced to avoid conflicts of interest when pressured for prescriptions by farmers.²⁴⁵ For that purpose IKB introduced in 2009 the prerequisite for livestock farmers to procure veterinary services and medicines from only one veterinary practice to reduce competition between veterinary practices.²⁴⁵

Also a compulsory post academic education for veterinarians was introduced (in 2011), as well as the development of specific treatment guidelines to support veterinarians in their clinical decision-making.

As in Belgium, Dutch veterinary practices have their own depot of veterinary medicines. This has been questioned in the public debate and at governmental level. However, the Dutch government concluded that this would not lead to a reduction in antibiotic use. Instead the economic motives to prescribe were expected to be greatly eliminated by the benchmarking of antibiotic prescription and use and the introduction of a strict one-to-one relationship between farmers and veterinarians.²⁴⁵

In 2014, new legislation has been introduced by the government, making veterinary intervention obligatory for the administration of antibiotics. Only under specific conditions, farmers are permitted to administer antibiotics to their animals without the physical intervention of a veterinarian. This new legislation promotes a one-to-one relationship and includes mandatory periodical herd inspections by a veterinarian.²⁴⁵

Apparently political and public pressure slowly changed farmers' attitude towards antibiotic use.²⁴⁵ Important in this changing attitude was the confrontation of farmers with isolation measures upon hospital admission of themselves or one of their family members because of a potential methicillin-resistant *Staphylococcus aureus* (MRSA) colonization.²⁴⁴

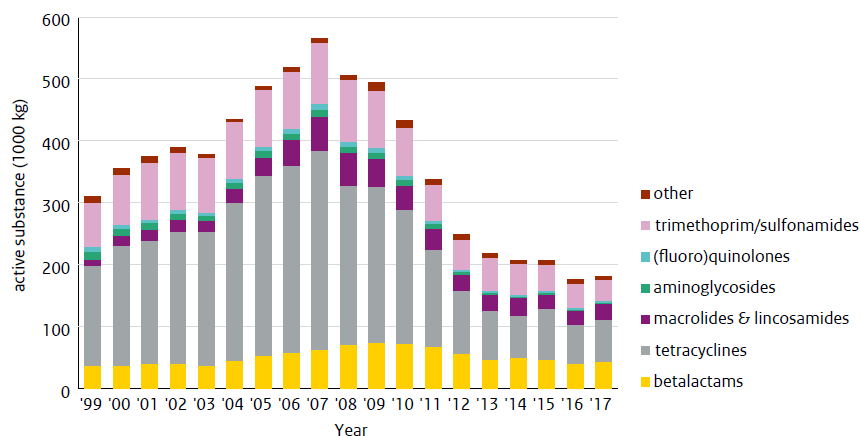
Dutch Monitoring of Antimicrobial Resistance and Antibiotic usage in animals in the Netherlands (MARAN)

Antibiotic usage and antimicrobial resistance in animals are closely monitored in the Netherlands; the data are published in the so called MARAN yearly reports (Monitoring of Antimicrobial Resistance and Antibiotic usage in animals in the Netherlands). They are based on sales data for all antimicrobial veterinary medicinal products on package level provided by the federation of the Dutch veterinary pharmaceutical industry ('Fabrikanten Importeurs Diergeneesmiddelen Nederland', FIDIN), supplemented with antimicrobial veterinary medicinal products data of non FIDIN members. The data are estimated to cover approximately 98% of all sales in the Netherlands.³⁸⁴



The 2018 MARAN report revealed that the sales of antimicrobial veterinary medicinal products had decreased in 2017 by 63.38% in comparison with the reference year 2009, indicating that the goal set for 2015 (i.e. a 70% reduction in 2015 compared to 2009) was not reached yet. The use of critically important antibiotics (especially 3rd and 4th generation cephalosporins) is reduced to an absolute minimum.³⁸⁴ Figure 21 presents the veterinary antimicrobial medicinal product sales in the Netherlands for the period 1999-2017.

Figure 21 – Antimicrobial veterinary medicinal product sales in the Netherlands, 1999-2017



Source: Reproduced from MARAN, 2018 ³⁸⁴

6.2.5.2 The Danish example

Ban on non-therapeutic use of selected antibiotics

Denmark was among the first countries to ban the use of antimicrobials for growth promotion and disease prevention in animal production. In 1995 non-therapeutic uses of avoparcin^{zzz} and in 1998 virginiamycin were discontinued. Subsequently (also in 1998) Danish producers agreed to voluntary ban all antimicrobials for growth promotion in dairy cattle, broiler chickens and the older swine (finishers). By the end of 1999 this was extended to young pigs (weaners).⁴²⁵ This made Denmark a pioneer country in Europe regarding prudent antibiotic use.⁴²⁶

The initial effect of the ban was a sharp decrease in antimicrobial use, as well as in the occurrences of antimicrobial resistance. However, the antimicrobial use for therapeutic purposes increased. Total antimicrobial use grew during the 2000s. The Danish Government began to use the VETSTAT (cf. infra) data to pressure veterinarians to reduce total antimicrobial prescription. In 2010 the Yellow Card scheme was introduced to decrease the use in the pig sector through the oversight of farmer prescription practices monitored through the VETSTAT data. Producers transcending a threshold level incurred a warning (yellow card) and got follow-up measures. This led to a 12.5% reduction in antimicrobial use in the second half of 2010 and even more in 2011.⁴²⁵

Restriction on antibiotic sales

Since 1990 Danish veterinarians can no longer sell antibiotics. Veterinarians may hold a stock of products obtained from a pharmacy, but may only in certain conditions supply products directly to the farmer for the treatment of animals under his care. Farmers can only obtain medicated feed from feed mills on veterinary prescription.⁴²⁶

Since 2000 any use or distribution of antibiotics, including medicated feed, must be recorded in an electronic register (i.e. VETSTAT). The veterinarian

^{zzz} It has been demonstrated that the animal use of avoparcin, a glycopeptide growth promoter, is, at least in part, responsible for the emergence of vancomycin-resistant enterococci in animals and the same vancomycin-

resistant clone of enterococci has been found in animals and humans.⁴²⁴ These findings have led to a ban on avoparcin in the European Union and a similarly acting product, virginiamycin, in Denmark.



does the registration for livestock, while pharmacies register antibiotic use in horses and companion animals. Herd owners must keep a diary concerning the animals treated, the drugs used, date and reason for treatment, dosage, administration route, responsible person and the origin of the drug.^{427, 428}

For livestock, antibiotics can only be used if the veterinarian has diagnosed an infection which justifies its use. Veterinarians may only on certain conditions supply or prescribe antibiotics which are administrated by the farmer (not the veterinarian), and the farmer must follow the veterinarian's advice and written instructions. Farmers can continue for a maximum of 5 days a therapeutic antibiotic treatment initiated by the veterinarian, except for adult cattle.⁴²⁸

In 2010 veterinary advisory service contracts (VASC) became mandatory for large herds of cattle and pigs, as well as for mink farms. These contracts comprise frequent veterinary advisory visits and provide the farmer with extended treatment possibilities. The focus is mostly on advice and prevention, rather than treatment. The aim is the optimization of antibiotic use.⁴²⁸

The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme

The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) was founded in 1995 as a unique One Health platform for the continuous surveillance and research of antimicrobial use and resistance. The aim is to provide an evidence base for decision-making and get insight into the associations between antimicrobial usage and AMR. In Denmark all prescriptions of antibiotics are recorded in national databases, MedStat for the human and VetStat for the animal sector.⁴²⁷ Note that VetStat not only includes livestock, but also companion animals.

In general DANMAP has demonstrated that curbing antibiotic use can result in the reduction of the resistance to very low levels, but a more typical outcome is the stabilisation of resistance levels (because of co-selection by other antimicrobials). Thus instead of actually lowering resistance, the Danish efforts primarily resulted in preventing a further rise.⁴²⁷

Overall, the use of antimicrobials for animals decreased by approximately 3% between 2016 and 2017. This decrease was mainly driven by the

reduced use of antimicrobials for pigs (about 4%).⁴²⁷ For the human sector, the ECDC 'Annual Epidemiological Report for 2017 - Antimicrobial consumption' (ESAC-Net) reveals that Denmark ranks among the 27 EU/EEA countries 10th with regard to the use of antibiotics for systemic use in the ambulatory sector (15.0 DDDs per 1000 inhabitants per day) and ranks 14th of the 22 participating EU/EEA countries with 2.07 DDDs per 1000 inhabitants per day in the hospital sector.⁸

Key messages

- **In the veterinary sector several policy measures, at the Belgian and European level, have been taken too restrict the use of antibiotics.**
- **The majority of the interventions undertaken in veterinary sector have not been evaluated so far.**
- **Yet, there is scientific evidence that the optimization of herd management, improvement of the biosecurity and guidance on prudent antibiotic use are promising routes of action to achieve the reduction of antibiotic use, without jeopardizing production results.**
- **In the Netherlands, political and public pressure slowly changed farmers' attitude towards a more prudent use of antibiotics. Important in this changing attitude was the confrontation of farmers with isolation measures upon hospital admission of themselves and their family members out of fear for a potential methicillin-resistant *Staphylococcus aureus* (MRSA) colonization.**
- **Denmark was among the first countries to ban the use of antimicrobials for growth promotion and disease prevention in animal production. It has a unique One Health platform for the continuous surveillance and research of antimicrobial use and resistance ('Danish Integrated Antimicrobial Resistance Monitoring and Research Programme', DANMAP). Antibiotic use in horses and companion animals is also registered.**



6.3 Other aspects to consider in developing interventions aiming to change prescription behaviour

The prescription and use of antibiotics are examples of behaviour and are driven by a large number of factors. Dozens of theories on behaviour and behaviour change have been developed across disciplines in social and behavioural sciences.⁴²⁹ Based on the 33 most relevant theories, the Theoretical Domains Framework has been developed, initially to identify **influences on health professional behaviour** related to implementation of evidence-based recommendations (Box 26).⁴³⁰ The framework provides a theoretical lens through which the cognitive, affective, social and environmental influences on behaviour can be seen. It comprises 14 domains; knowledge is only one domain, representing only one driver or group of drivers of social behaviour.⁴²⁹⁻⁴³¹

Box 26 – Domains of the Theoretical Domains Framework

- | | |
|---|--|
| • Knowledge | • Intentions |
| • Skills | • Goals |
| • Social/professional role and identity | • Memory, attention and decision processes |
| • Beliefs about capabilities | • Environmental context and resources |
| • Optimism | • Social influences |
| • Beliefs about consequences | • Emotion |
| • Reinforcement | • Behavioural regulation |

Source: Davis et al., 2015,⁴²⁹ Atkins et al., 2017,⁴³⁰ and Michie et al., 2018⁴³¹

Still, most interventions aiming at a more prudent antibiotic prescribing focus on knowledge and awareness raising, through e.g. media campaigns, peer education, training, feedback on prescriptions. They assume that if prescribers and patients are informed about the consequences of non-prudent antibiotic prescription and use, they will change their behaviour accordingly. This approach tends to oversee that knowledge does not automatically translate in behaviour change.⁴³² There are a number of psychological (e.g. risk avoidance, feelings of uncertainty), social (e.g.

reputational risks, consulting etiquette, professional identity and criteria for being judged a good clinician) and institutional (e.g. peer practice norms, time pressure, institutional hierarchies) barriers, which are much more difficult to change than an individuals' stock of knowledge.⁴³³ The role of knowledge in behaviour change is by far overestimated.

Although we know from the vast body of literature on the determinants of antibiotic prescribing and use that antibiotic prescribing is a multilevel and multidimensional phenomenon (see Chapter 5), many determinants are not considered when developing interventions and action plans. This means that a **huge number of potential drivers of behaviour change** is yet **unexplored** in the search for effective ways to improve antibiotic prescription and use.

Moreover, despite a large knowledge base in social and behavioural sciences on the drivers of behaviour and behaviour change (see the Theoretical Domains Framework above), research on the determinants of antibiotic prescribing and use is mostly descriptive. Sociological theoretical frameworks however can be very useful in the research on antibiotics prescription and use, especially in generating hypotheses and searching for explanations. The same accounts for macro-sociological theories, on e.g. the medical profession, welfare state regimes, health care systems. **Involving social and behavioural scientists** in the **research** on antibiotic prescription and use, as well as in **policy development**, may create new insights and ideas for **more effective interventions**.

In addition, antibiotic prescription and use are **wicked problems** (see Box 27) and should be treated as such. In Chapter 5 we listed and described the determinants of antibiotic prescribing and use as they are reported in the literature. However, to merely list the determinants and use them as a list of independent variables is deceptive. We should be aware that these **determinants interact** and are entangled in **complex webs** that **change over time**.⁴³⁴ The systems map (see chapter 7) takes these interdependencies into consideration; it acknowledges the complexity of antibiotic prescription and use. When addressing a wicked problem such as antibiotic prescribing and use, good results depend on bringing in as **many perspectives** as possible. Hence, systems thinking points out the need for collaboration.⁴³⁵ This need implies that traditional bureaucracies characterised by vertical silos (divisions based on specialised knowledge on



one topic or part of the problem) are not well-adapted to address wicked problems such as antibiotic prescribing and use.⁴³⁶

Last but not least, antibiotic prescription and use are **highly context specific**. Therefore interventions, tackling non-prudent use should also be tailored to specific contexts, both at country and institutional level. One size does not fit all in the case of antibiotic prescription and use. **Copy paste of policy measures** which proved to be effective in promoting prudent antibiotic prescribing and use in other countries will **not be a guarantee for success in Belgium**. When developing a national action plan to decrease non-prudent antibiotic prescription and use, the specificity of the Belgian culture and the health care system should be taken into account. Some structural measures (e.g. increasing the number of days sickness leave without certification by a doctor, restriction of the free choice of GP) are expected to have a high impact on antibiotic prescription and use, but are very controversial.

7 STAKEHOLDER CONSULTATION AND SYSTEMS MAPPING

Authors: Philippe Vandebroeck (shiftN), Kim Becher (shiftN), Randy Mellaerts (shiftN)

7.1 Introduction

The present chapter describes the stakeholder engagement process. The aim was to consult key stakeholders and collect suggestions for improvement of antibiotics policy and of interventions for prudent antibiotics' prescription and use. As was explained before, the research wants to reflect the One Health principle that sees human, animal and environmental health as inextricably linked. As a result, this project also includes animal use of antibiotics in its scope, but due to man-power and time constraints the environmental aspect was left out of scope.

7.2 Approach

For the stakeholder consultation process a systems thinking approach was applied. This was operationalised as a qualitative approach based on a 'systems mapping' methodology. The basic idea underpinning the research methodology is that a shared view of the complex interdependence of factors that contribute to inappropriate prescription and use patterns in the animal and human sectors would lead to a more balanced and informed assessment of stakeholders of appropriate measures to take.⁴³⁷ The approach was informed by an awareness that the challenge of improving antibiotics policy, and patterns of prescription and use, has the character of a 'wicked problem' (see Box 27). These are policy challenges that show a high degree of technical and social complexity and as a result are particularly resistant to final solutions. Systems thinking and dialogue are key elements of an approach to ground a social learning process around wicked issues.⁴³⁸ Consultation of key stakeholders in this research was deemed necessary to better understand actors' basic assumptions and the values and norms in which they are embedded. Furthermore, active involvement of stakeholders in identifying recommendations for policy would likely increase their support for these measures and increase their political viability. Finally, group-based



processes of collective inquiry enhance the mutual understanding of worldviews in complex multi-stakeholder settings.⁴³⁹

Box 27 – What are wicked problems?

Wicked problems have distinctive characteristics. First, they have no clear definition, as **different stakeholders have different views** on what the problem is. Second, wicked problems are **multi-causal** and have **many interdependencies**. Different stakeholders place **different emphasis** on the various causal factors. Because of the interdependencies, addressing wicked problems leads to unintended consequences elsewhere. Third, wicked problems are constantly evolving, hence policy makers focus on a **moving target**. Since the problem is constantly evolving, there is no definitive solution. Work on a wicked problem is not terminated for reasons inherent to the logic of the problem, but because of external reasons such as running out of time or money. Fourth, there are no criteria that tell that the solution has been found. Solutions are not true or false but rather better or worse, or satisfying. Also **solutions cannot be tested**: after being implemented a solution will generate waves of consequences over an extended period of time. Fifth, there are not opportunities for trial-and-error, as every solution to a wicked problem is a one-shot operation. There is no 'undo-button' for wicked problems. Sixth, wicked problems are **unique**: solutions that worked well for one wicked problem are not likely to be effective for another wicked problem. Seventh, a wicked problem is often a **symptom of a higher-level problem**. Wicked problems stand out in **social complexity**, rather than technical complexity. They are never bounded to the responsibility of one organisation or organisational level. Solutions to wicked problems **involve sustained behavioural change of individual citizens**.^{436, 440}

The research was conducted between November 2017 and July 2018:

- Stakeholder consultation through face-to-face in-depth interviews with a balanced sample of key representatives from the veterinary, human ambulatory and hospital sectors;
- Synthesis of stakeholder views in a systems map;
- Internal review of the systems map;
- Stakeholder review of the systems map in a first workshop;
- Second stakeholder workshop, with the systems map as an aid, to collect suggestions for improvement of the Belgian antibiotics policy and of interventions for prudent antibiotics' prescription and use.

This chapter is structured as follows:

- Section 7.3 zooms in on the *systems mapping approach*, with focus on the nature of systems maps, their syntax, use and analytic potential, and the particular status of the systems map in the framework of this research project.
- Section 7.4 discusses the *process* that led to the development of the systems map and the suggestions for improvement of antibiotic policy derived thereof.
- Section 7.5 is dedicated to the *results* of this research. It includes a description of the systems map and the inventory of suggestions offered by stakeholders for improvement of antibiotics policy and of interventions for the prudent antibiotics prescription and use.
- In sections 7.6 and 7.7 the above results are discussed and conclusions are formulated.



7.3 Systems map

7.3.1 Concept and syntax of the systems map developed in this research

Systems map is a generic label for a broad class of visual representations of complex systems or of the way they are perceived by human beings. By the notion of *system* we understand “a *structured set of objects and/or attributes together with the relationships between them*”.⁴⁴¹ The constitutive elements of a system are, therefore, 1) its elements, 2) the relationships between these elements and 3) the system boundary that distinguishes between what does and does not belong to the set.

A systems map can take different forms. In this research we relied on a particular form of a so-called *directed graph*. A graph is in its most general sense a representation of a network, i.e. a set of nodes in which some pairs of the nodes are linked to one another. In a directed graph the connections have a direction associated to them (say, if there is a connection between node A and node B, then this connection will be denoted as being ‘from A to B’, or vice versa).

Graphs can represent all kinds of networks. In this research the systems map is a network of concepts. The concepts are derived from statements made by stakeholders in an interview setting. The relationships between the concepts are understood as ‘influences’. So a connection between concepts A and B indicated by an arrow that starts in A and directed towards B, is understood as concept A having an influence on concept B. In that case we also refer to A as the ‘tail concept’ (as it is located at the tail of the arrow) and B as the ‘head concept’.

For example, a concept (A) derived from an interviewee statement might be the following: “Access to trusted sources of scientific expertise”. Another concept (B) might be: “Practitioner expertise regarding prudent prescription of antibiotics”. The connection between A and B, visualised by an arrow going from the former to the latter, then means: “*The degree to which practitioners have access to trusted sources of scientific expertise influences their level of expertise regarding prudent prescription of antibiotics.*” (see Figure 22)

Figure 22 – An influence link between two concepts



All concepts have been *expressed as variables*, meaning that they can move over a scale, increasing to higher levels or decreasing to lower levels. Adding ‘the level of ...’ or ‘the degree to which ...’ to the concept reinforces that sense of variability. For instance, the concept ‘Fragmentation of infectiology teaching base’ should be properly read as ‘the degree to which the infectiology is fragmented’ or ‘level of fragmentation of infectiology teaching base’.

In this map a distinction is made between *three types of connections*:

- *Positive connections*: a positive connection, indicated by a blue arrow, means that an increase in the ‘tail concept’ (A) is believed to lead to an increase of the ‘head concept B’. And vice versa: if the level of A decreases, then the level of B decreases.
- *Negative connections*: a negative connection, indicated by a red arrow, reverses the direction of influence. An increase in the tail concept leads to a decrease of the head concept and vice versa.
- *Neutral connections*: in a few cases, the direction of influence can go both ways. So B may increase or decrease depending on how A increases. Then the arrow has a grey colour.

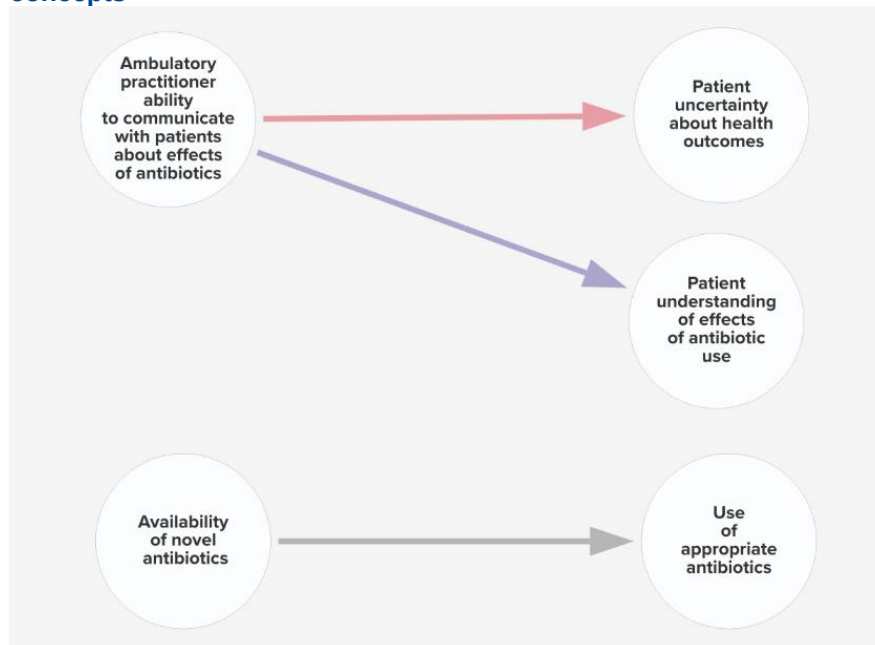
Examples of each type of connection are shown in Figure 23:

- If ambulatory practitioners’ ability to communicate with patients about the effects of antibiotics increases, then we can expect patients’ uncertainty about health outcomes to decrease (red arrow) and patients’ understanding about the effects of antibiotic use to increase (blue arrow).



- The degree to which novel antibiotics are available may have a beneficial or detrimental influence on the (level of) appropriateness of antibiotics use, depending on how their use adequately matches the therapeutic context. In other words, the use of late-generation antibiotics may or may not be justified in view of existing guidelines.

Figure 23 – Positive, negative and neutral connections between concepts



Clearly, a connection's characterisation as positive or negative is not an absolute given. It depends on the way the concepts have been phrased. For instance, if in the figure above, the head concept would have been phrased as 'Patient *confidence* about health outcomes', then the link between the head and tail concepts would have been positive, as the practitioners' communication skills are expected to reinforce patients' confidence. So the arrow would have been coloured blue.

No assumptions have been made about relative differences in the strength of the influence of A concepts on B concepts. Although theoretically feasible, no weight has been attributed to connections.

To sum up, the syntax of the systems map developed in this research process contains two elements: concepts, and connections between concepts. Concepts are understood as variables. Connections denote an influence from a tail concept on a head concept. The direction of this influence can be aligned in the two concepts, or not.

7.3.2 The status of the systems map

Given the syntax and conceptualisation of the systems map discussed above we are now in a position to situate the map within the range of established systems maps formats. We submit that the map relied on in this research has a hybrid character, reflecting elements of a causal loop diagram, a cognitive map, an influence diagram and a mind map.

- A *causal loop diagram* shows the array of 'influences' or 'causes' that drive a system's behaviour. The syntax used in the present systems map is fully aligned with the syntax of a causal loop diagram.
- A *cognitive map* is a network coded from what a person says: "A cognitive map is a model (...) designed to represent the way in which a person defines an issue. It is not a general model of someone's thinking, neither is it intended to be a simulation model of decision making. It is a network of ideas linked by arrows." ⁴⁴² The present systems map aligns with this methodological principle in that it has been developed from oral statements made by stakeholders in response to questions that are pertinent to the scope of the research. So, the systems map reflects the concepts that stakeholders rely on when they are invited to talk about friction points in the Belgian antibiotics policy and prescription and use culture. However, the systems map differs from a cognitive map as it represents not an individual but an aggregate perspective of the interviewed sample of stakeholders.



- An *influence diagram* visualises the relationships between elements of a decision problem^{aaaa}. It depicts key elements, including decisions, uncertainties and objectives as nodes and the influences among them as arrows. The present systems map could be read as an influence diagram. A significant subset of the concepts used in the map can be interpreted as decision points, i.e. variables that can be modified (by actors at different levels of decision making, be it national, regional, interorganisational, intra-organisational and as an individual) to achieve a desired objective (in this case the overall objective is to increase the prudence of prescription of antibiotics for animals and humans). For instance when 'Funding of sensitisation campaigns' is positively linked to 'Effectiveness of sensitisation' campaigns, then the tail concept could be seen as a decision variable that could be leveraged by the relevant funding authority. Some concepts in the present map are of a more contextual nature. For instance, the 'Complexity of the Belgian political landscape' is a given rather than a feature that can be modified by any actor in the short term. In the present map decisions have not been visually distinguished from context elements and desired objectives.
- A *mind map* is a generic format to visually organise information. A distinctive feature of a mind map is its hierarchical, radial (tree-like) structure around a central concept.⁴⁴³ Nodes in the mind map are connected by lines that can mean different things, for instance 'concept A belongs to the class of concepts B', or 'concept A is related to concept B'. In actual practice, given the rather loose syntax, there is a lot of freedom in developing mindmaps. The present systems map could be read as a mind map organised around the central concept of 'Antimicrobial resistance' and developed based on a rigorous syntax in which all nodes are 'concepts as variables' and connections always denote a relationship of influence. We can also add that most published mind maps remain relatively simple and include relatively few nodes and hierarchical levels. They are used as an aid in brainstorming and note-taking. The present map is in comparison rather complex.

To conclude: the systems map developed in this research shows a kinship with several known classes of directed graphs. Based on its syntax one might consider it as a special case of a causal loop diagram. In its representation of stakeholder opinions it partakes of the character of a cognitive map. As the visual structuring of a decision problem it presents itself as an influence diagram. Finally, it can also be seen as a specific example of the more generic class of mind maps. In its hybrid character it reflects the aims and approach of this research project.

7.3.3 Use of systems maps

As can be deduced from the discussion in the previous section, systems maps can serve different purposes:

- In general, as conceptual models, systems maps are used as tools for *knowledge representation and learning*. Their synthetic nature and streamlined syntax make them particularly suitable for showing 'the big picture'. This is particularly useful in dealing with complex decision-making challenges that spill over into different policy domains and scientific disciplines. In this research project it was quite key to be able to generate a perspective on the challenge of supporting an effective antibiotics policy that transcended the niches of policy makers, actors in the human sector (ambulatory and hospital-based professionals), and actors in the veterinary sector. Furthermore, the integrated character of the systems map reinforced the felt need to approach the research question from a One Health perspective that sees human and animal health as inextricably linked.
- As a result of their integrated, cross-disciplinary character, systems maps may become potent vehicles to *support multi-stakeholder engagement and collaboration*. A 'big picture' conceptual model provides a canvas for bringing different stakeholders together in focused and disciplined interactions. In this research project the **systems map was used to bring a variety of stakeholders together**

^{aaaa} What is an influence diagram? Available at: <http://www.lumina.com/technology/influence-diagrams/> (last access: 16 January 2019)



to reflect on approaches to improve antibiotic policy or improve antibiotic prescription and use. The issue was politically sensitive and as a rule stakeholders had strong opinions about the reasons for existing challenges and appropriate strategies to move ahead. Therefore it was important to frame the debate in a way that could be perceived to be neutral and reflecting the concerns of different stakeholders. The systems map was consciously developed based on neutral concepts, that did not articulate a problem, or put blame on a certain stakeholder. **In principle each concept in the map is a candidate intervention point to improve the system.** For instance, one of the concepts mentioned in the map is the 'Quality of academic training on prudent use of antibiotics'. The map merely states that this has been mentioned as a factor that may help or hinder in creating an appropriate level of expertise about appropriate prescription of antibiotics. It helps if the quality is high (as the level of expertise is expected to increase as well) and it hinders when the opposite is true. However, the map does not state that the quality of academic training on prudent use of antibiotics is *insufficient* (although some stakeholders were of the opinion that this was the case, mainly because of the fragmentation of infectiology teaching base). Phrasing it as a quality deficiency may, however, lead certain actors (say, academic administrators, or professors) to take a defensive position. This could lead to an unproductive debate about perceived truths. By simply indicating that quality of academic training is a factor that affects the level of expertise and hence contributes to prudence of antibiotic prescription, stakeholders perceived the discussion environment as 'no blame' which is a key group decision making value.⁴⁴⁴ As a result an open discussion was possible on all concepts included in the map as a starting point for possible interventions for improvement.

- The systems map was developed with the help of a web-based visualisation platform (Kumu, see <https://kumu.io>). **Each element of the systems maps can be documented with meta-data**, turning the maps into portals to interactively explore a potentially extensive database. In this research project this was only a secondary objective given that the map was to a very large extent based on qualitative data collected via stakeholder interviews. Intentionally, this report does not include an inventory of the coded interview material, not even in an anonymised format, to make sure that interviewees could not be identified. In view of the relatively modest size of the interview sample, the use of Dutch and French as native language of the interlocutors and the easily detectable professional background of the interviewees, it is impossible to guarantee their anonymity as was agreed with all of them prior to the interview. Given the political sensitivity of this research, protection of anonymity seemed a key requirement to maintain productive post-project stakeholder relationships.
- Systems maps are effective tools for the communication of important and complex messages throughout a decision-making process and particularly in the reporting and delivery phase. Customised versions of the systems maps can help to communicate the findings of the project to a broader audience. The present systems map offers that potential too. Its mere complexity and scope already signals the multidimensional nature of the policy challenge.

To summarise: throughout this work, the systems map's function is two-fold; first, its analytic function is to provide us with an overview of interdependent elements (derived from qualitative, stakeholder input) that shape the current state of antibiotic policy, prescribing and use in Belgium. In that sense, it is the result of data collection and analysis. Second, it served the process of stakeholder involvement in the sense that it facilitated stakeholders to formulate improvements to the current situation.



7.4 Methods

7.4.1 Selection of stakeholders

A longlist of stakeholders was drawn up capitalising on the familiarity of KCE with the human-oriented part of the Belgian antibiotics-related stakeholder arena. Targeted research completed the longlist with representatives from the veterinary sector. The longlist was reduced to a shortlist of 25 candidate interviewees. The shortlist sought to balance several criteria:

- Sector: human and veterinary
- Language/region: French and Dutch-speaking part of the country;
- Professional role/position in the field: professionals from the field, academics, representatives from the public services, BAPCOC and other involved organisations. Within the human sector: representation of the hospital and ambulatory sector;
- Within the hospital sector: representation of academic and peripheral hospitals.

Altogether, these criteria sought to maximise representativeness in a rather heterogeneous stakeholder field composed of professional and sectorial subgroups. Eventually the number of interviews came down to 19. However, given the presence of a number of 'double interviews' (with two interviewees) and one with three spokespersons, the total number of people involved settled on 24. This group was composed as follows:

- 11 representatives from the human sector, 9 from the animal sector and 4 from the pharmaceutical sector;
- 17 Dutch-speaking and 7 French-speaking stakeholders. (The imbalance was most pronounced in the representatives of the animal sector of which only 2 were French-speaking);
- Within the human sector 3 spokespersons represented a policy perspective; 2 general practitioners, 1 ambulatory practitioner with an hospital practice, and 5 hospital-based practitioners;

- The animal sector was represented by 3 people with a regulatory role, 3 veterinarians, 2 producers (1 pig and 1 fish farmer) and 1 feed company sector representative.

In preparation of this politically sensitive research project, members of the KCE research team went out to discuss the focus of the research with a significant number of stakeholders. The purpose of these conversations was to better understand expectations, sensitivities and viewpoints. The insights extracted from the preliminary interviews were broadly informative for the whole report; more precisely they were essential for the identification of important stakeholders, the development of the interview guides and the systems mapping work package as a whole. However, the interviews were not fully transcribed and they were not included in the coding that formed the basis for the development of the systems map.

The full list of stakeholders who were interviewed by KCE, by shiftN and/or who participated in one of the workshops (cf. infra) and their affiliation can be found in the colophon of this report.

7.4.2 Interview guide

The scope of the interviews had to match the objectives of the research project, namely to solicit suggestions from stakeholders for improvement of antibiotics policy and interventions to improve prudent antibiotics prescription and use. As a result the scope of the interviews had to encompass the full breadth of the Belgian practice related to regulation, prescription and use of antibiotics, related to humans and animals. The interview guide was developed through an iterative process going back and forth between the KCE and shiftN team. It was semi-open and structured around a number of key questions and a larger number of subsidiary questions tailored to specific subsectors (veterinary, human-ambulatory, human-hospital). The first few interviews were considered as a pilot to check whether the guide worked well and indeed some questions had to be adapted, deleted and amended to fully cover the scope of the interview. The key and additional questions included in the interview guides can be found in Appendix 1.



Interviews were executed by 2 researchers from the shiftN-team, one for the Dutch speaking interviewees, one for the French speaking. Double interviews were done by the two interviewers together.

7.4.3 Coding of interviews

Interviews were fully transcribed, resulting in a text corpus of more than 300 pages of interview material. This material was then coded by a single researcher-analyst to maximise consistency. The approach used was closely related to 'causation coding^{bbbb}' as this matches the basic cause-and-effect logic embodied by the systems map. More specifically we coded the data for linked tail concepts (antecedents) and head concepts (outcomes).

The logic of this coding approach fits the scope of this research well as the systems map aimed to visualise stakeholders' perceptions on the workings of the Belgian antibiotic system and the way it enabled or hindered prudent prescription and use. In line with Maxwell's recommendation the coding tried not to fragment the data but to extract processual links embedded within extended excerpts.⁴⁴⁷ Connecting back to the concepts shown in Figure 23, a coding example based on an interview excerpt originally recorded in Dutch (own translation into English) is provided in Box 28. A description of the systems map is provided in section 7.5.1.

Box 28 – Coding example

"I've learned that you should never tell someone ... suppose you enter with a fever. I examine you and I don't detect anything and I say "It's nothing". That's wrong. Now I'm saying when I'm dealing with a child: "I have checked this and this and this and I don't see anything special. This will be the next step and probably it will be this, so I am not going to prescribe you antibiotics. But if it gets worse you have to come back." And if you have a flu as an adult and you don't want to talk to me I will examine your ear and throat and I will do this and that and that and I don't find anything. And you may leave and think "I have the flu ... doesn't he notice?" No, I can't see that. And if you explain this to people than they will understand that. But the way of communicating and explaining things to people. And never close the door. Always leave the door open, and if it gets worse you just come back. Even if it's the same day. Or if you see something change."

From this excerpt we initially extracted the tail concept *Ambulatory practitioner communication skills* and the head concept (outcome) *Patient uncertainty about health outcomes*. As the patient uncertainty decreases as communication skills increase these concepts are linked by a 'negative connection' (i.e. a red arrow in the systems map).

This example is emblematic for a significant part of the interview material that had a colloquial character and required considerable effort to interpret and synthesize into concepts to be included in the systems map (a practical challenge was the requirement to limit the concepts to a maximum of 100 characters, including spaces, to maintain readability of the systems map).

^{bbbb} Saldaña, 2013 ⁴⁴⁵ quotes Munton et al., 1999⁴⁴⁶: "Causation coding attempts to label the mental models participants use to uncover 'what people believe about events and their causes ... An attribution is an expression of the way a person thinks about the relationship between a cause and an outcome.'" Additionally Saldana holds: "Causation Coding is appropriate for discerning motives (by or toward something or someone), belief systems, worldviews, processes, recent histories, interrelationships, and the complexity of

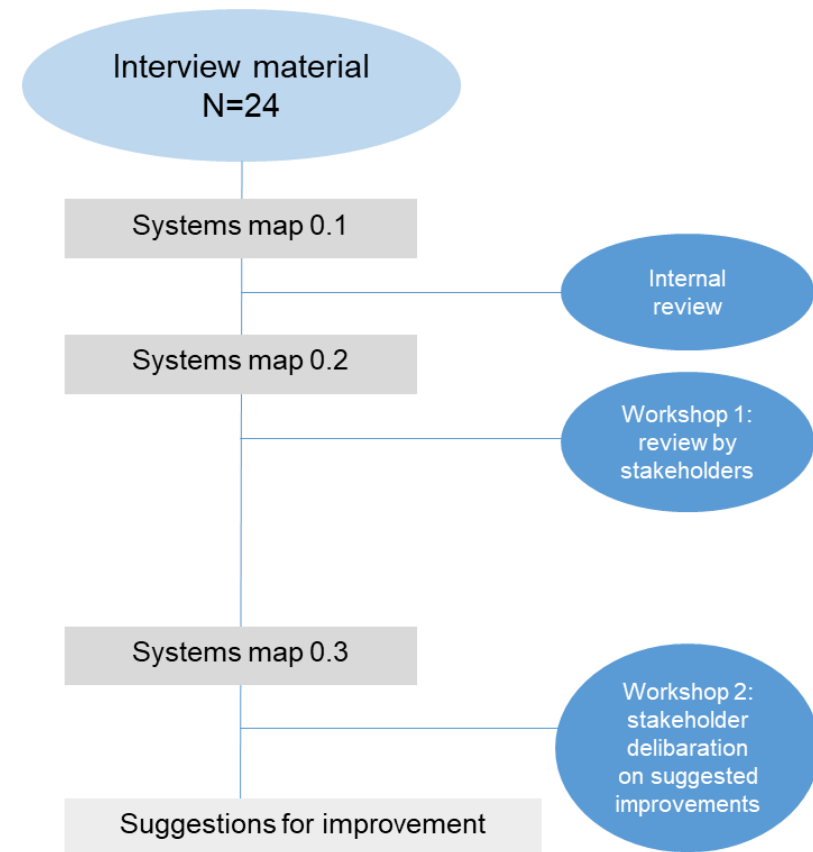
influences and effects on human actions and phenomena. The method may serve grounded theorists in meticulous searches for causes, conditions, contexts, and consequences. The method is also appropriate if you are trying to evaluate the efficacy of a particular programme, or as preparatory work before diagramming or modeling a process through visual means such as decision modeling and causal networks."⁴⁴⁵



7.4.4 Internal review of the systems map

The coding of the interview material led to a preliminary version of the systems map (version 0.1; see Figure 24). In preparation for a first stakeholder workshop this was scrutinised by the KCE members of the research team. Based on the insights extracted from the preliminary round of interviews with key stakeholders, the ongoing literature search for determinants of antibiotics prescription behaviour and the reading of the mapping interview material, a total of 43 suggestions were made to amend the systems map. The suggestions fell into different groups: addition of new concepts from the mapping interview material, addition of linkages between concepts already included in the systems map, and suggestions to rephrase a number of concepts for the sake of clarity. So, these suggestions mainly had a bearing on the micro- and meso-level architecture of the map. The macro-architecture was not put into question. The suggestions were processed by the shiftN members of the research team, which led to version 0.2 of the systems map, which was subsequently submitted to stakeholders in an interactive workshop (cf. infra). After the workshop another internal review round was organised to make sure that the stakeholder input was faithfully translated into the systems map (version 0.3). This version was used as input to a second stakeholder workshop in which stakeholders were invited to formulate suggestions for improvement.

Figure 24 – Data collection process





7.4.5 Stakeholder review of the systems map

A first workshop was organised to present the systems map to stakeholders and to provide them with an opportunity to suggest improvements^{cccc}. Invited to the workshop were all stakeholders who had been involved in the mapping interview campaign. In addition, a subset of people who were interviewed by KCE were also invited. The workshop was attended by 20 people (8 French speaking and 12 Dutch speaking).

The discussion was organised in three subgroups: one group was asked to focus on the animal area of the map (attended by 5 participants), one group to focus on the human ambulatory area (attended by 7), and one group on the human hospital area (attended by 8). In addition, all groups were asked to consider the policy and market-related clusters as well (see section 7.5 for a description of the systems map).

The discussion during the workshop was open and lively. As a result, 82 suggestions for improvement of the map were offered. Again, these had a bearing on the micro- and meso-level architecture of the map, with suggestions for rephrasing, additional connections and a number of additional concepts. All in all the systems map was welcomed as comprehensive and faithfully reflecting the views of the stakeholders. The macro-architecture of the map was not put into question.

7.4.6 Stakeholder deliberation on suggested improvements of antibiotics policy

A second workshop was focused on the identification of suggestions to improve antibiotic policy or interventions to improve prudent antibiotic prescription and use^{dddd}. All stakeholders who had been invited for the first workshop were also invited to the second workshop. The workshop was attended by 23 people, 14 of them had also attended the first workshop. Again there was a reasonably balanced attendance of representatives of both veterinary (n=7) and human sectors (ambulatory: n=8, hospital sector: n=8). The systems map was handed out to all participants (as a collection of A3 prints) as an aid in this reflection. The results of a brainstorm in each

subgroup (animal, human hospital, human ambulatory) was shared with the plenary and discussed. In a final stage of the workshop participants were handed five coloured stickers which represented 'votes'. They were asked to prioritise suggestions for improvements by allocating their five votes to one or more suggestions offered by any of the subgroups. The result was a prioritised inventory of suggestions for improvement that covered the whole antibiotics system.

7.5 Findings

In this section we describe the main features of the systems map and discuss the improvements suggested by the stakeholders. We provide a reading guide to the systems map which is a textual translation of the map.

7.5.1 Main features of the systems map

The systems map is composed of 236 concepts and 364 connections between concepts. The map reflects a visual and conceptual hierarchy: the concepts are grouped in 13 thematic clusters, identified by colour. Clusters emerged inductively: concepts were extracted from the interview material and those that were considered to belong together were subsequently grouped under one label. Clusters group concepts that relate to key actors and settings in the antibiotics systems ('Farmers', 'Veterinarians', 'Antibiotic stewardship teams', 'Ambulatory practitioner-patient relationship'), policy effectiveness and policy instruments ('Policy', 'Guidelines', 'Campaigns', 'Veterinary sector autoregulation', 'Veterinary sector regulation'), and other drivers ('Expertise and reflexivity', 'Market', 'Livestock business model'). A 'Core' cluster was identified that provides the conceptual backbone of the systems map. The main reason for introducing this visual and conceptual hierarchy is to make the map easier to read.

^{cccc} Organised on 7 May 2018 at KCE offices.

^{dddd} Organised on 11 June 2018 at KCE offices.



Further, within each cluster a distinction is made between key concepts (blue colour) and secondary concepts (coloured by cluster). Key concepts were loosely identified as concepts with 'a lot of arrows coming in and going out'. A table with all concepts, structured in line with the visual hierarchy, can be

found in Appendix 5.1 to this report (Table 56). In Table 57 in Appendix 5.2 all connections between the elements are presented. Table 47 includes the clusters, their key concepts and the number of secondary concepts for each cluster.

Table 47 – Clusters and key concepts of the systems map

Cluster	Key concepts	# secondary concepts
Core	Antimicrobial resistance Appropriateness of animal AB consumption Appropriateness of human AB consumption Prudence of AB prescription for humans Prudence of AB prescription for animals Use of appropriate ABs Presence of ABs in the environment Volume of AB in waste water streams Extent of human migratory flows	
Policy	Coherence of AB policy Effectiveness of AB policy Effectiveness of intersectoral coordination	23
Campaigns	Effectiveness of sensitisation campaigns	12
Ambulatory relationship	practitioner-patient Strength of independence of AP in relation to patient Assertiveness of patient demand for ABs Patient understanding of effects of AB use	27
Expertise and reflexivity	Practitioner expertise regarding prudent AB use Readiness of APs to question AB prescribing behaviour Weight of high volume prescription culture	26
Guidelines	Effectiveness of implementation of AB prescribing guidelines	21
Stewardship teams	Effectiveness of AB stewardship teams in hospitals	22
Market	Price of ABs Availability of old ABs	11
Farmers	Farmers' receptiveness to guidelines for prudent AB use	13



Cluster	Key concepts	# secondary concepts
	Strength of historical recommendations for use of AB	
Veterinarians	Prudence of veterinary AB prescription	13
	AB prescribing-related economic interest of veterinarians	
	Vets' receptiveness to AB prescribing guidelines	
Vet sector autoregulation	Effectiveness of sector's autoregulation	11
	Willingness of feed companies to support AB auto-regulation	
Vet sector regulation	Enforceability of regulation of vet AB use	5
Livestock business model	Pressure on profitability	17
	Availability of cost-efficient, profitable alternative treatments	
	Risk of disease	

AB: antibiotics; AP: ambulatory practitioner; #: number

Visually the map can be divided into two main parts: a top part devoted to the prescription and use of antibiotics in the human sector and a bottom part devoted to the prescription and use of antibiotics in the animal sector. The two parts connect to the core concept 'Antimicrobial resistance'.

The map is complex chiefly because of the large number of concepts included. But there are few feedback loops, leading to a structure in terms of clusters that are relatively clearly demarcated and easy to read in their hierarchical structure of key vs. secondary concepts. The weak feedback structure of this particular map is a contingent result of this particular research. It does not compromise the value of the systems map in this research trajectory.

Section 7.5.2 includes a cluster-by-cluster reading guide for the systems map. The reading guide is a synthetic, narrative equivalent of the systems map. However, it is not able to do fully justice to the richness of the underlying data. A certain loss of nuance is inevitable. Its aim is merely to help orient the reader of the systems map.



7.5.2 Description and presentation of the systems map

The size of the map does not allow to print it legibly on an A4 sheet. The minimum printing size for practical use is A0. To make the reading of the map possible in this report, it was divided into 16 figures according to the 13 thematic clusters:

- Figure 25 – Core of the systems map – part 1 & Figure 26 – Core of the systems map – part 2
- Figure 27 – Stewardship teams in hospitals
- Figure 28 – Antibiotic policy
- Figure 29 – Sensitisation campaigns
- Figure 30 – Antibiotic prescription guidelines & Figure 31 – Antibiotic prescription guidelines (veterinary)
- Figure 32 – Practitioner expertise and reflexivity
- Figure 33 – Ambulatory practitioner-patient relationship
- Figure 34 – Market of antibiotics
- Figure 35 – Veterinary sector autoregulation
- Figure 36 – Farmers
- Figure 37 – Livestock business model 1 & Figure 38 – Livestock business model 2
- Figure 39 – Veterinarians' antibiotic prescription practices
- Figure 40 – Veterinary sector regulation

In addition, a high-resolution A0-sized version is available separately as an addendum to this report, downloadable from the KCE website. The map can also be explored interactively via this url: https://tools.kce.be/systems_map/antibiotics/.

The text below provides a concise cluster-by-cluster reading guide to the systems map. Each cluster can be located with reference to the figures on which the cluster concepts can be found (Figure 25 to Figure 40). Concepts included in the map are referenced in *italic* between square brackets.

Cluster: Core

The Core cluster forms the backbone of the systems map on which all other clusters are grafted (Figure 25, Figure 26). The cluster revolves around the central concept of [*Antimicrobial resistance*]. Mitigation of antimicrobial resistance hinges on the [*Appropriateness of human antibiotic consumption*] and [*Appropriateness of animal antibiotic consumption*]. Appropriateness of consumption is driven by efforts to increase [*Prudence of antibiotic prescription for humans*] and [*Prudence of veterinary antibiotic description*]. These five key concepts are the basic causal nexus of the systems map. They can be found centrally located in the map. Only [*Appropriateness of animal antibiotic consumption*] was placed much lower in the animal part of the map to enhance readability.

Directly connecting to the concept [*Prudence of antibiotic prescription for humans*] are a large number of concepts:

- [*Weight of high volume prescription culture*] (key concept in Cluster: Expertise and Reflexivity, Figure 25);
- [*Practitioner expertise regarding prudent AB use*] (key concept in Cluster: Expertise and Reflexivity, Figure 25);
- [*Readiness of ambulatory practitioners to question antibiotic prescription behaviour*] (key concept in Cluster: Expertise and Reflexivity, Figure 25);
- [*Effectiveness of antibiotic policy*] (key concept in Cluster: Policy, Figure 25);
- [*Strength of ambulatory practitioner independence in relation to patient*] (key concept in Cluster: Ambulatory Practitioner-Patient relationship, Figure 25);
- [*(Assertiveness of) Patient demand for antibiotics*] (key concept in Cluster: Ambulatory Practitioner-Patient relationship, Figure 25);
- [*Likelihood of antibiotic prescription by other ambulatory practitioners*] (concept in Cluster: Ambulatory Practitioner-Patient relationship, Figure 33);
- [*Access to and correct use of rapid diagnostic aids*] (concept in Cluster: Ambulatory Practitioner-Patient relationship, Figure 33);



- [*Impact of fee for service reimbursement*] (concept in Cluster: Ambulatory Practitioner-Patient relationship, Figure 33);
- [*Frequency of consultation*] (concept in Cluster: Ambulatory Practitioner-Patient relationship, Figure 33);
- [*Emergency visits in ambulatory and hospital care*] (concept in Cluster: Ambulatory Practitioner-Patient relationship, Figure 33);
- [*Propensity of ambulatory practitioners to avoid short term patient risk*] (concept in Cluster: Ambulatory Practitioner-Patient relationship, Figure 33);
- [*Access to patient medication history*] (concept in Cluster: Ambulatory Practitioner-Patient relationship, Figure 33).
- [*Practitioner identification with expert status*] (concept in Cluster: Expertise and Reflexivity, Figure 32);
- [*Ambulatory practitioner understanding of detrimental effects on individuals and population of long-term antibiotic use*] (concept in Cluster: Expertise and Reflexivity, Figure 32);
- [*Antibiotics as convenient, accepted reinforcement of expert status*] (concept in Cluster: Expertise and Reflexivity, Figure 32);
- [*Ability to impose restrictions on 'empirical prescriptions'*] (concept in Cluster: Expertise and Reflexivity, Figure 32).

We refer to the descriptions of the corresponding clusters for context. There is one additional factor which feeds into [*Prudence of antibiotic prescription of humans*]: [*Use of appropriate antibiotics*](Figure 25). This is upstream connected to [*Availability of old antibiotics*] (concept in Cluster: Market, Figure 34), [*Availability of novel antibiotics*] (concept in Cluster: Market, Figure 34), [*Prescription incentives from antibiotic producers*] (concept in Cluster: Expertise and Reflexivity, Figure 32), and [*Access to lab results*] (concept in Cluster: Stewardship teams, Figure 27).

There are also exogenous factors that contribute to the rise of [Antimicrobial resistance], notably the increasing [Extent of human migratory flows] and the [Presence of antibiotics in the environment]. The latter is driven by [Volume of antibiotics in waste water streams] (due to careless waste disposal and animal and human faeces). Also the physical proximity of humans to pets (for which often inappropriate antibiotics are prescribed) is a risk factor. (Figure 25, Figure 26)

Concepts feeding into [Appropriateness of animal antibiotic consumption] are the following (Figure 26):

- [Farmers' receptiveness to guidelines for prudent antibiotic use] (key concept in Cluster: Farmers, Figure 36);
- [Risk of disease] (key concept in Cluster: Livestock business model, Figure 37);
- [Availability of cost-efficient, profitable alternative treatments] (key concept in Cluster: Livestock business model, Figure 37);
- [Prudence of veterinary AB prescription] (key concept in Cluster: Veterinarians, Figure 39);
- [Enforceability of regulation of veterinary antibiotic use] (key concept in Cluster: Veterinary sector regulation, Figure 40);
- [Preventative animal consumption of medicated animal feed] (concept in Cluster: Veterinarians, Figure 39);
- [Availability of benchmarking] (concept in Cluster: Farmers, Figure 36);



Figure 25 – Core of the systems map – part 1

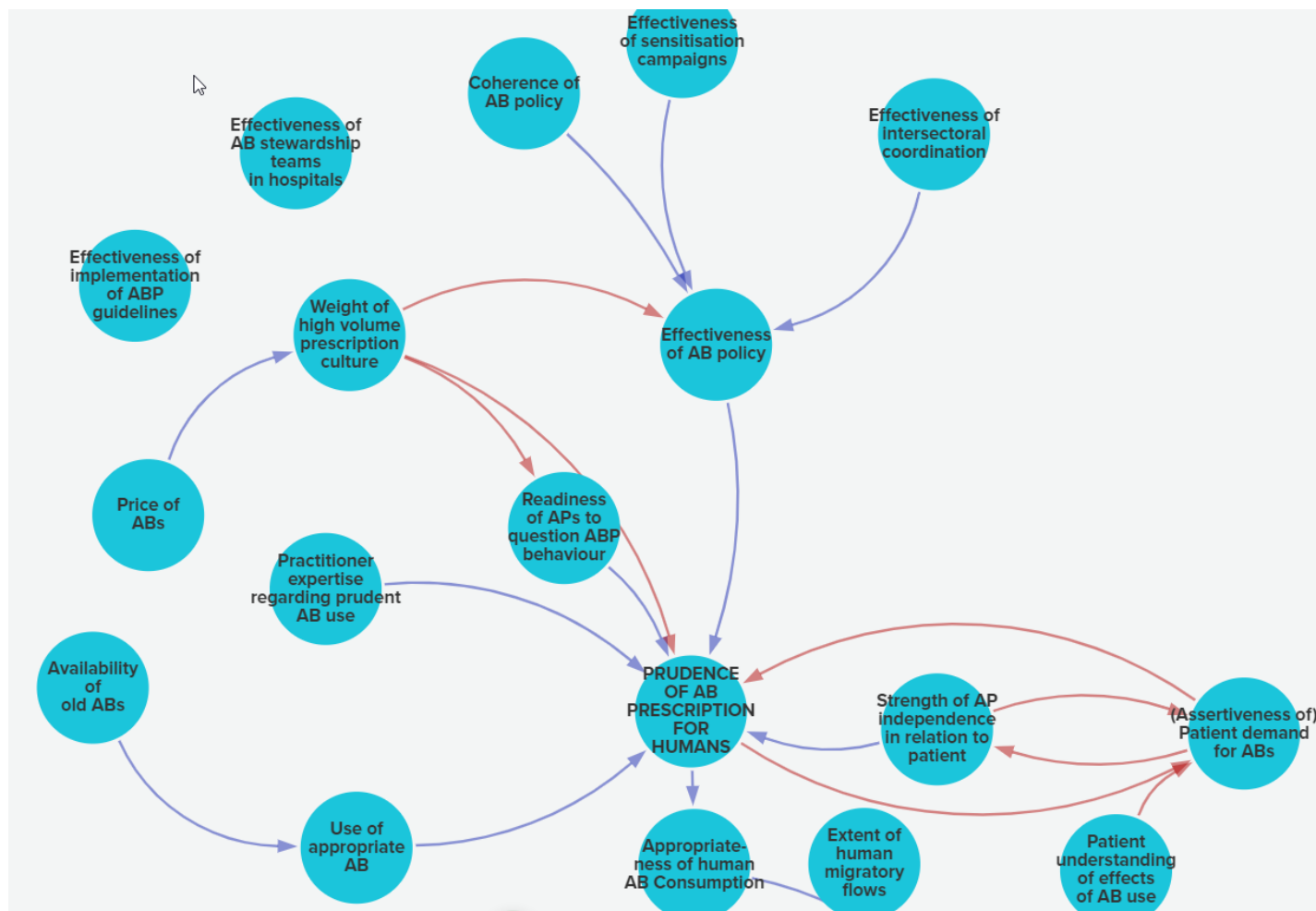


Figure 26 – Core of the systems map – part 2





Cluster: Stewardship teams in hospitals

The key concept (blue circle) in this cluster is [*Effectiveness of antibiotic stewardship teams in hospitals*]. Although the minimum composition, mandate and tasks of hospital antibiotic stewardship teams have a legal basis (since 2008) the operational effectiveness of these teams depends on a large number of factors that reflect the complexity of the social and professional environment in hospitals (Figure 27).

- Effectiveness of stewardship teams is predicated on a productive collaboration between clinicians and hospital infectiologists^{eeee}. However, the [*Receptiveness of clinicians to direct interference by infectiologists*] tends to be low. Given that [*Approval of infectiology and medical microbiology as medical specialties*] in Belgium is still outstanding, the [*Assertiveness of infectiologists and medical microbiologists*] too claim their proper role in stewardship activities is often lacking. The effectiveness of stewardship teams would also be enhanced by active [*Collaboration between antibiotic stewardship teams and Hospital Hygiene Teams*]. In practice these entities are often working independently. Also, the ability to influence the prescribing behaviour of individual doctors in a hospital depends on their relationship with the hospital (salaried employee or independent) [*Ability of hospital management to influence MD prescribing*] (Figure 27).
- Also financial factors come into play [*Funding of in-hospital AB stewardship teams*]. Stakeholders judge this funding as modest. It doesn't cover all expenses (for instance, compensation of a hospital pharmacist for antibiotics management is not included). Some stakeholders argue to ensure a [*Coupling of hospital financing to antibiotic prescription-related quality indicators*] (pay-for-quality). This would lead to more [*Political leverage over allocation of antibiotic stewardship team funding*] and would ensure active [*Support from hospital management*], lending more [*Authority to antibiotic stewardship teams*]. At present, given the modest funding, clinicians make a lot of

contributions to stewardship activities on a voluntary basis. As a result the [workload of in-hospital antibiotic stewardship teams] is high (Figure 27).

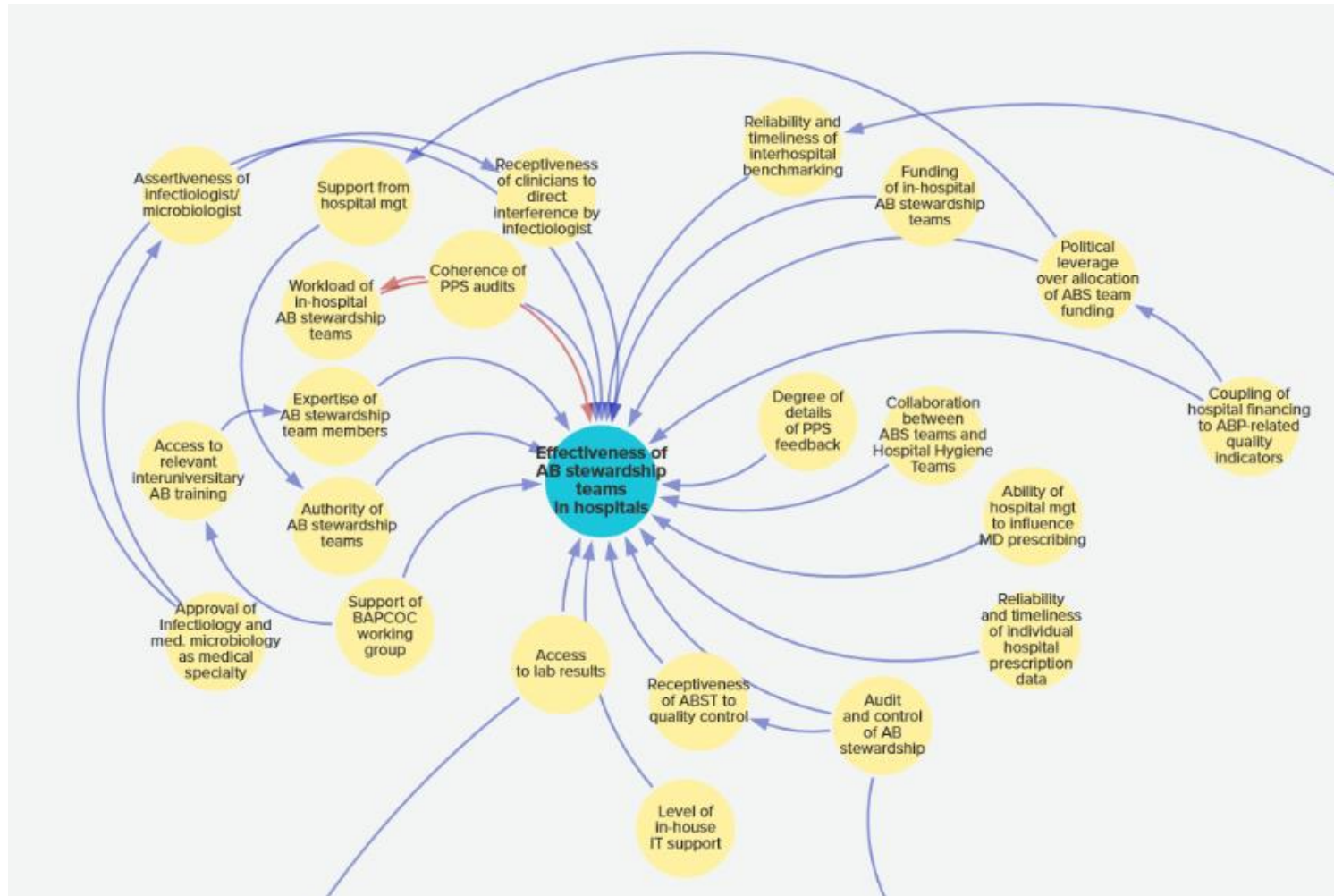
- The level of [Expertise of antibiotic stewardship team members] is another determinant of team effectiveness. Stakeholders point to a lack of [Access to relevant interuniversity antibiotics-related training]. This would hinge on active [Support of the relevant BAPCOC working group] (Figure 27).
- Stewardship teams need access to various sources of data to operate effectively: quick [Access to lab results] to take clinical decisions, and, at a higher level of aggregation: hospital prescription data [Reliability and timeliness of individual hospital prescription data], interhospital benchmarks [Reliability and timeliness of interhospital benchmarking], and feedback on their own effectiveness [Audit and control of AB stewardship]. Comparisons between hospitals are fraught with practical difficulties. Comparative data are published with a delay so that professionals feel they are always looking in the rear-view mirror to adjust their team's performance. Currently there is a limited control on the performance of stewardship teams. However, not all teams are equally keen on being audited [Receptiveness of antibiotic stewardship teams to quality control]. Access to all these data revolves on an appropriate [Level of in-house IT support] (Figure 27).
- One of the tasks that falls to antibiotic stewardship teams is the participation in Point Prevalence Surveys (PPS). For hospital stewardship teams a PPS is a considerable investment of resources. It adds considerably to the [Workload of in-hospital antibiotic stewardship teams]. Results of ECDC PPS are also becoming slowly available and are not detailed enough to provide actionable feedback to hospital teams [Degree of details of PPS feedback]. There is also the 'global PPS' that is less resource intensive, quicker to execute and provides more timely feedback to participating hospitals. However, it is important that there is [Coherence between PPS audits] (Figure 27).

^{eeee} This medical specialty is mentioned in the Royal Decree of 2008 (available at:

http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=fr&la=F&cn=1991030433&table_name=loi, yet it is not officially recognised yet in 2018.



Figure 27 – Stewardship teams in hospitals





Cluster: Antibiotic policy

In this prominent and spread-out cluster there are three key concepts (blue circles): [*Effectiveness of antibiotic policy*], [*Coherence of antibiotic policy*], [*Effectiveness of intersectoral coordination*]. The latter two feed directly into policy effectiveness (Figure 28).

[*Coherence of antibiotic policy*] is negatively influenced by the [*Complexity of the national antibiotics institutional landscape*]. Stakeholders note that there is a proliferation of antibiotics-oriented initiatives and studies, piloted by different actors at the national and international level [*Proliferation of AB-oriented initiatives*]. It is hard to maintain an overview of and maintain the coherence between everything that is going on. Policy coherence is also dependent on the availability of appropriate consumption and surveillance data as a basis for allocation of resources. This pivots on appropriate data management [*Centralisation of epidemiological data*], [*Access to an integrated set of indicators*] (also reflecting a One Health approach), and the [*Ability to unambiguously determine consumption levels*] of antibiotics. As regards the latter, it transpires from the interviews with stakeholders that there seems to be disagreement about the selection of measurement unit to be used (i.e. Defined Daily Dose (DDD) vs. packages etc.). This issue is further elaborated in section 4.1.1.

[*Effectiveness of intersectoral coordination*] is an important determinant of the [*Effectiveness of antibiotic policy*]. In Belgium the coordination falls to the Belgian Antibiotic Policy Coordination Committee (BAPCOC, see section 3.4.2.2).

- According to stakeholders, the complexity of the institutional environment in which BAPCOC operates [*Complexity of Belgian political landscape*], [*Complexity of host public service FOD – SPF*] negatively influences the effectiveness of intersectoral coordination. One of the problems that BAPCOC is faced with is limited [*Ability to flexibly allocate funding to interventions*]. Funding may be available, but it takes a lot of time and efforts to actually mobilise resources. Another feature of this institutional environment is the necessity to work in a bi-lingual context. Not all experts contributing to BAPCOC activities are equally fluent in French and Dutch [*Bi-lingual skills of experts and professionals*] which hampers the committee's effectiveness. Finally, stakeholders assess the [*Visibility of BAPCOC*] as being too low which reduces its impact (Figure 28).

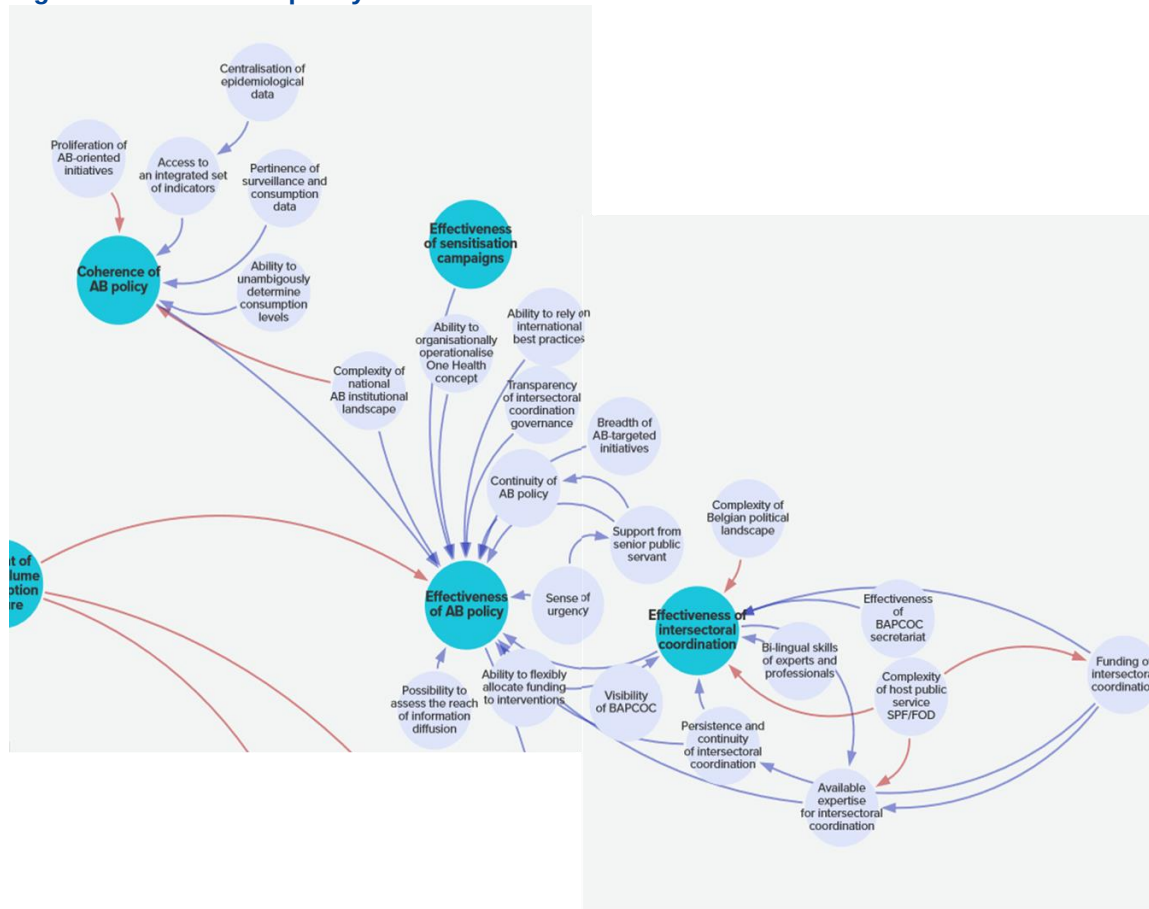
- The [*Effectiveness of the BAPCOC secretariat*] has vacillated over the years due to understaffing and personnel changes (Figure 28).
- Some stakeholders are of the opinion that there is insufficient [*Funding of intersectoral coordination*]. Expert contributions are largely voluntary which makes it hard to attach sufficient [*Expertise for intersectoral coordination*]. It also affects the [*Persistence and continuity of intersectoral coordination*] (Figure 28).

The third key concept is [*Effectiveness of antibiotic policy*] to which the other two key concepts in this cluster contribute.

- Stakeholders are of the opinion that Belgian antibiotic policy should focus on long-term continuity of interventions that are known to be effective, in Belgium and abroad [*Continuity of antibiotic policy*], [*Ability to rely on international best practices*]. On the other hand, antibiotic policy needs to cover a wide range of interventions. The [*Effectiveness of sensitisation campaigns*] is an important determinant of policy effectiveness but it is not enough. Therefore, adequate [*Breadth of antibiotic-targeted initiatives*] is key to an effective policy (Figure 28).
- Intersectoral coordination is an important vehicle for policy development and implementation. Issues that affect the [*Effectiveness of intersectoral coordination*] also have an impact on [*Effectiveness of antibiotic policy*]. Some stakeholders think that the governance of the BAPCOC is not transparent enough. To them it is unclear how mandates are filled and decisions are taken [*Transparency of intersectoral coordination governance*] (Figure 28).
- Antibiotic policy is, in principle, conceived with a 'One Health' concept in mind. However, in practice it has been difficult to organisationally embody that leading idea. BAPCOC hosts an expert group on veterinary medicine. However, within the animal sector the 'centre of expertise' AMCRA (Antimicrobial consumption and resistance in animals) plays a leading role in initiating efforts that contribute to a rational use of antibiotics. BAPCOC and AMCRA have shared objectives and they do collaborate but institutionally and organisationally they operate along different models. According to stakeholders this makes it hard to really operationalise the 'One Health' principle in antibiotic policy [*Ability to organisationally operationalise a One Health concept*] (Figure 28).



Figure 28 – Antibiotic policy



- The degree to which the political and professional communities that are dealing with antibiotic policy share a [*Sense of urgency*] has a positive influence on effectiveness of antibiotic policy. Stakeholders think that this sense of urgency is not shared widely enough. Also the [*Support from senior public servants*] is important to make antibiotic policy work (Figure 28).
- Two concepts that reflect the professional culture into which antibiotic policy has to intervene feed directly into [*Effectiveness of AB policy*]: [*Weight of a high volume prescription culture*] (see cluster: Expertise and Reflexivity, Figure 32) and [*Practitioner receptiveness to guidelines for antibiotic use*] (see cluster: Guidelines, Figure 30).

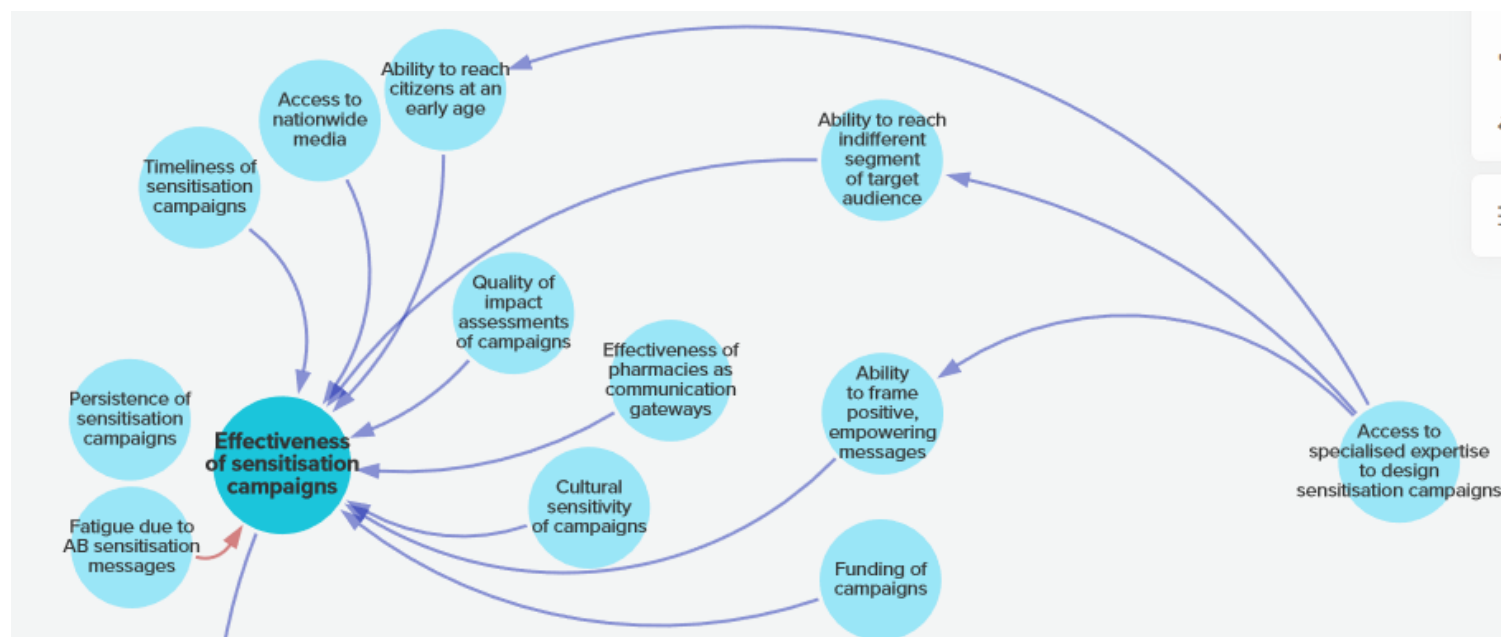


Cluster: Sensitisation campaigns

The key concept is *[Effectiveness of sensitisation campaigns]*. Sensitisation campaigns towards the general public have been a persistent feature of Belgian antibiotic policy. However, their effectiveness has been blunted by a certain fatigue of the target audience towards campaign messages *[Fatigue due to antibiotic sensitisation messages]*. In addition, there is a segment of the population that remains indifferent to sensitisation efforts *[Ability to reach indifferent segment of target audience]*. Some stakeholders are convinced that in order to lend more impact to campaigns they ought to be managed in a more disciplined way *[Timeliness of sensitisation campaigns]*, *[Persistence of sensitisation campaigns]*, *[Quality of impact assessments]*, *[Persistence of sensitisation campaigns]*, *[Quality of impact assessments]*, *[Quality of impact assessments]*

assessment of campaigns]. Also campaigns need to be designed differently: more pointedly culturally sensitive, targeted towards citizens at an early age and built around positive, empowering messages *[Cultural sensitivity of campaigns]*, *[Ability to reach citizens at an early age]*, *[Ability to frame, positive, empowering messages]*. New communication gateways need to be leveraged *[Effectiveness of pharmacies as communication gateways]*, *[Access to nationwide media]*. This requires access to financial resources and specialist expertise that are not always available *[Funding of campaigns]*, *[Access to specialised expertise to design sensitisation campaigns]* (Figure 29).

Figure 29 – Sensitisation campaigns





Cluster: Antibiotic prescription guidelines

The key concept in this cluster is [*Effectiveness of implementation of antibiotic prescription guidelines*] (Figure 30). This applies mainly to the development and use of guidelines within hospitals and to a lesser extent to the ambulatory sector. The factors related to the use of guidelines in the animal sector have been included in the discussion of the Veterinarians cluster below (Figure 31).

- Hospitals are required (by royal decree) to issue their own guidelines for antibiotic prescription. High-quality guidelines (that are coherent, evidence-based, up to date) are more effectively implemented [*Quality of hospital antibiotic prescription guidelines*] (Figure 30).
- As a rule these guidelines are based on existing national (or international) guidelines that have been adapted to the Belgian situation. Hence, the quality of these national guidelines is important [*Quality of national AB prescribing guidelines*]. Stakeholders pointed out that adequate funding available for development and regular updating of national guidelines has been found lacking [*Funding for guideline development*]. Stakeholders also think it is advisable to stay away from industry financing for reasons of objectivity and continuity^{ffff} [*Independence from industry funding*] (Figure 30).
- Stakeholders also note that there have been multiple initiatives to develop guidelines at national level (for hospital and ambulatory sector) and that there was a lack of coherence between these guidelines. [*Coherence amongst national guidelines*], and [*Coherence between national and internal guidelines*] positively affect the effectiveness of implementation of prescription guidelines (Figure 30).
- Prescription guidelines have to be accessible, practical and user-friendly to facilitate effective implementation [*Practitioner access to AB prescribing guidelines*], [*Practical workability of AB prescribing*

guidelines]. Stakeholders note that there are ambiguities and (sometimes inevitable) gaps between the guidelines and the reality on the floor. Computer-based solutions allow for tighter [*Cross-therapeutic integration of AB guidelines*]. As regards accessibility, there are complaints about the [*Accessibility and visibility of the BAPCOC website*] (Figure 30).

- The [*Quality of the (internal) guideline development process*] also affects the effectiveness of their implementation. It is advisable that practitioners are able to actively contribute to the process [*Possibility of practitioners to contribute to guideline development*]. Some (but certainly not all) stakeholders are of the opinion that also the involvement of pharmaceutical companies can be beneficial given their first-hand knowledge about the products prescribed [*Possibility of pharma companies to contribute to guideline development*] (Figure 30).
- A key element that influences the effectiveness of guideline implementation (and is influenced by it) the [*Practitioner receptiveness to guidelines for prudent antibiotics use*] (Figure 30). Many factors play into this: psychological [*Information overload of medical practitioners*] (see cluster: expertise and reflexivity, entire map) (which tends to be high), professional [*Practitioners' insistence on therapeutic freedom*] (see cluster: expertise and reflexivity, entire map) (which tends to be high), [*Clinical interest of antibiotics of medical practitioners*] (see cluster: expertise and reflexivity, Figure 32) (which tends to be low), and financial factors [*Financial incentives based on benchmarking of prescription behaviour*] (Figure 30), [*Coupling of hospital financing to AB prescribing-related quality indicators*] (see cluster: stewardship teams, Figure 27). As regards these financial incentives at practitioner and hospital level: these are currently very weak and many stakeholders believe that more significant incentives would have a beneficial impact on practitioners' receptiveness to guidelines for antibiotics prescription (Figure 30).

^{ffff} Companies may withdraw support at short notice because of commercial motives.



Figure 30 – Antibiotic prescription guidelines (human)

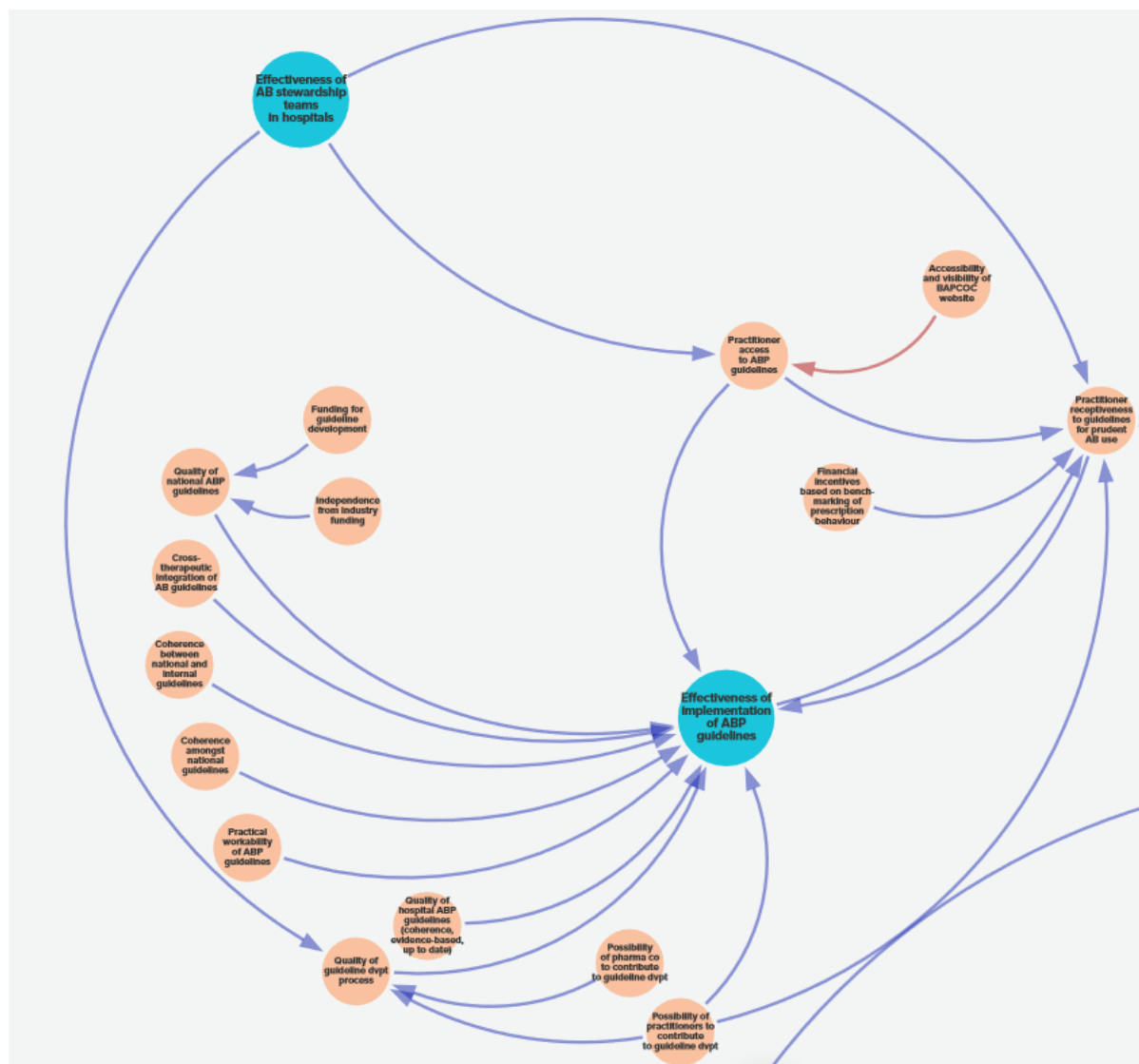
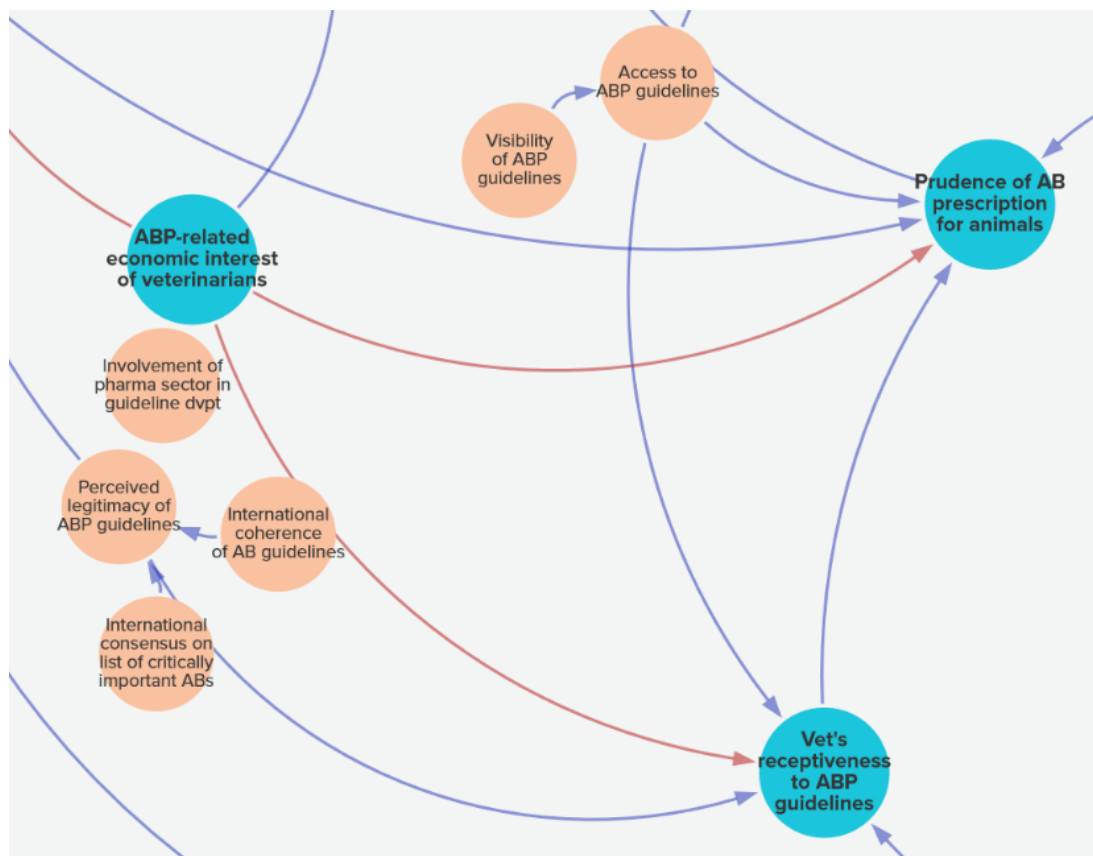




Figure 31 – Antibiotic prescription guidelines (veterinary)





Cluster: Practitioner expertise and reflexivity

There are three key concepts (blue circles) in this centrally located cluster: *[Practitioner expertise regarding prudent AB use]*, *[Readiness of APs to question antibiotic prescription behaviour]* (which is what is meant by 'reflexivity'), and *[Weight of high volume prescription culture]*. In general, it articulates the role of practitioners' expertise and prescription culture in prudent prescription of antibiotics (Figure 32).

[Practitioner expertise regarding prudent AB use] is negatively influenced by *[Years of practice]*. In addition, feeding into the key notion are multiple concepts that refer to sources of information that can help practitioners to develop a more prudent pattern of antibiotic prescription.

- The *[Quality of academic training on prudent antibiotics prescription]* is the basis for practitioners' expertise regarding prudent use of AB. Stakeholders comment that the quality of this training leaves something to be desired due to the *[Fragmentation of the infectiology teaching base]* over different subdisciplines (Figure 32). This is a result of the fact that infectiology is not recognised as a separate discipline *[Approval of infectiology and medical microbiology as medical specialty]* (see cluster: stewardship teams, Figure 27).
- Ambulatory practitioners need to have the opportunity to access pertinent and reliable antibiotics-related information and receive personalised feedback to support their practice. An important source of information and peer review are local quality circles ('Lokale Kwaliteitsgroep' – 'Groupe Local d'Évaluation Médicale', LOK – GLEM) to which practitioners have to adhere to keep their accreditation. So the *[Quality and availability of information to LOKs – GLEMs]* is an important determinant of practitioner expertise. In practice there is no requirement that quality circles focus on the topic of antibiotics prescription or that practitioners attend these sessions when they are organised (they need to attend two sessions per year). Some stakeholders think that focus on antibiotics prescription should be a mandatory part of the teaching agenda of these quality circles. Also better use should be made of the *[Possibility to receive feedback and discuss best practices with peers]* (in LOKs – GLEMs and also elsewhere). Finally, care should be taken to avoid that prescription-related information is filtered because of

involvement or sponsorship of pharmaceutical companies *[Prescription incentives from AB producers to reduce AB prescription]* (Figure 32).

- *[Clinical interest of antibiotics to medical practitioners]* is not always high. Incentives to continue to inform themselves could be coupled to professionals' obligation to maintain accreditation to practice. The RIZIV – INAMI collects individual prescription profiles of all professionals. Conditions for continued accreditation could be coupled to these prescription profiles *[Incentives associated to individual prescription profiles]*. Accreditation modalities could also be used to incentivise practitioners to continue to invest in 'life long learning' *[Incentives via accreditation for 'life long learning']* (Figure 32).
- From 1 January 2020 practitioners are obliged to use electronic prescription forms. This, in principle, could have offered opportunities to collect data on how antibiotics are prescribed in relation to the diagnosis made *[Use of electronic prescription system to collect AB prescribing data, incl. diagnosis]*, but for the moment no diagnosis has to be registered. Stakeholders consider this a missed opportunity. For practitioners it would create a *[Possibility to have personalised, authoritative feedback on antibiotic prescription behaviour]*. This would enhance practitioner expertise regarding prudent antibiotic prescribing (Figure 32).
- Stakeholders also pointed to other sources of information and feedback that could meaningfully contribute to practitioners' expertise: it would help if ambulatory practitioners could have *[Access to hospital-led infection prevention networks]*. Also *[Availability of tailored epidemiological data]* was mentioned as an aid to more informed prescription of antibiotics. Finally, at present there is very little *[Crossfertilisation between human and veterinary expertise]* as regards the effects of antibiotic use (Figure 32).
- *[Practitioner expertise regarding prudent AB use]* feeds directly and positively into the key concept *[Prudence of antibiotic prescription for humans]* (Figure 32).



- *[Practitioner expertise regarding prudent AB use]* also positively influences the *[Self-confidence of ambulatory practitioner]* (concept in the Cluster: Ambulatory Practitioner-Patient relationship, Figure 33). Finally it leads into the concept *[Ambulatory practitioner understanding of detrimental effects on individuals and populations of long-term antibiotic use]* (Figure 32).

A second key concept is the *[Readiness of ambulatory practitioners to question their antibiotic prescription behaviour]*. This reflexivity is partly driven by culture and partly by available information and feedback.

- There is a generational effect. Younger practitioners are on the whole more aware of the importance of prudent antibiotics prescription *[Age of ambulatory practitioner]*. Also, the importance that people associate with their role as expert may impede to question their own behaviour *[Practitioner identification with expert status (ego)]*. In general, the *[Weight of a high volume prescription culture]* is still significant (see further) (Figure 32).
- Stakeholders refer to other European countries (e.g. France, Sweden) where practitioners are incentivised financially to change their prescription behaviour *[Financial incentives to ambulatory practitioners to reduce antibiotics prescription]*. *[Incentives associated individual prescription profiles]* and the possibilities of providing practitioners feedback via the *[Use of electronic prescription system to collect antibiotic prescription data]* were already mentioned above. Finally, *[Practitioner acceptance of formal audits]* might also render them more willing to question their antibiotic prescription behaviour. Stakeholders mention that, for instance, there is very little oversight as regards prescription behaviour of practitioners in elderly homes. However, from the interviews it seems that there is no consensus on the appropriateness of formal audits (Figure 32).

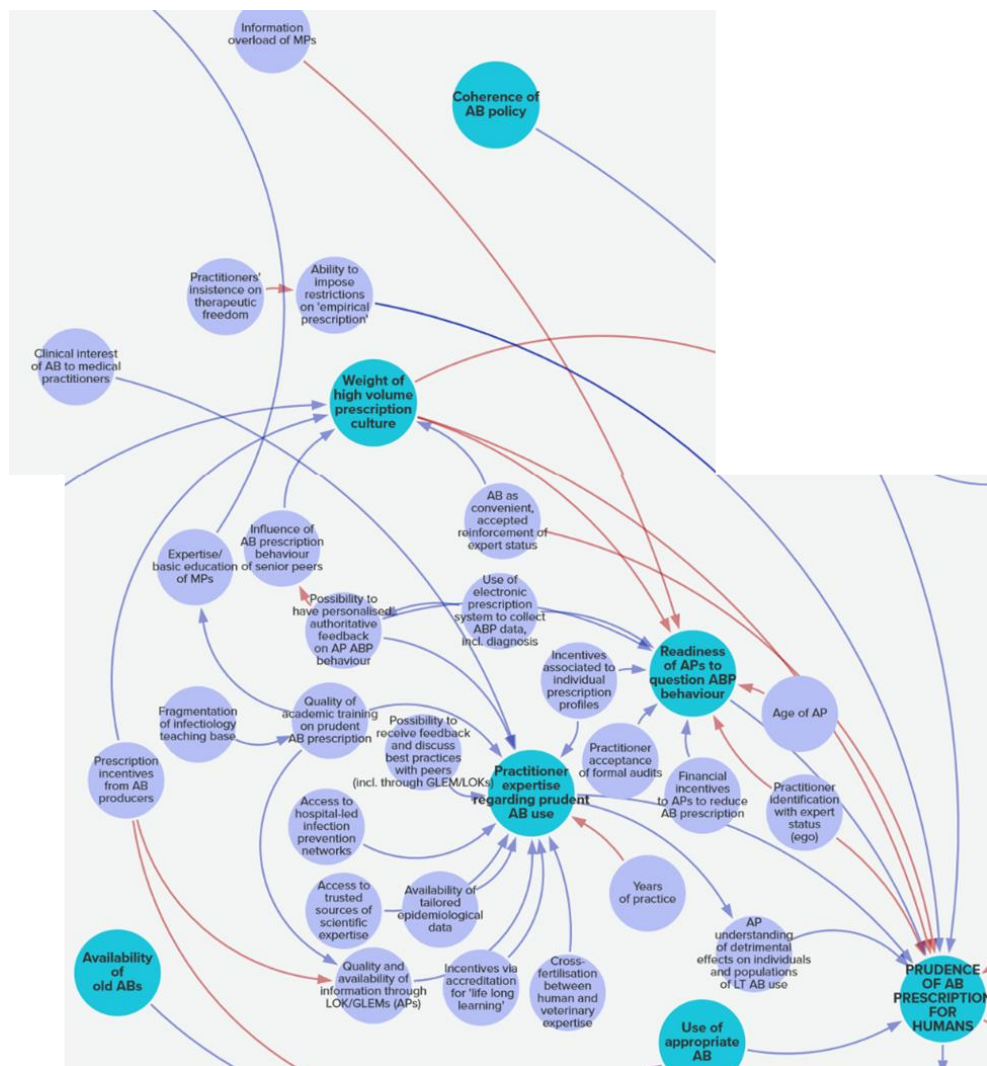
- Too much information can also be a problem. Practitioners have to process a large amount of information every day and this *[Information overload of medical practitioners]* influences their readiness to question themselves in a negative way.

Third and final key concept in this cluster is the *[Weight of a high volume prescription culture]*. Historically there has been a culture of medicalisation. Doctors prescribing pills informed by their own expert judgment was the therapeutic norm. Medicines, including *[Antibiotics (acted) as a convenient, accepted reinforcement of expert status]*. Younger practitioners are more aware of the need for prudence when prescribing antibiotics. Still, they may experience the *[Influence of the antibiotic prescription behaviour of their senior peers]* (Figure 32).

Finally, to these clusters belongs the concept *[Ability to impose restrictions on 'empirical prescription']* that feeds directly into the core concept *[Prudence of antibiotic prescription for humans]*. Empirical prescription is the practice of prescribing without diagnostic aids such as blood tests. These aids could be made mandatory for prescription of certain classes of antibiotics. However, these restrictions are met by resistance because of *[Practitioners' insistence on therapeutic freedom]*. Stakeholders also point out that this could lead to an increase of hospitalisations (Figure 32).



Figure 32 – Practitioner expertise and reflexivity





Cluster: Ambulatory practitioner-patient relationship

A first key concept is the [(Assertiveness of) Patient demand for antibiotics].

It is quite customary for patients to expect their GP or dentist to prescribe antibiotics. This is a manifestation of a culture in which consumption of antibiotics has become the norm [Weight of antibiotic consumption culture]. Some patients have an insufficient level of health literacy manifested in a limited knowledge of common complaints, a distrust of their proper healing resources, and an unwillingness to deal with uncertainty of health outcomes [Patient knowledge of common complaints], [Degree to which patients trust their medicines rather than their own healing resources], [Patient uncertainty about health outcomes]. Emotional factors come into play, particularly given parents' feelings of responsibility for their children, or working citizens feel they have to perform [Sense of responsibility of parents towards children], [Pressure on citizens to perform]. Financial considerations need to be considered as well: in return for their out-of-pocket expenses for a consultation some patients also feel entitled to demand from their practitioner what they seem as a desirable course of action [Patient out-of-pocket expense per consultation]. The prescription of antibiotics carries limited financial repercussions for patients [Cost to patient of antibiotics]. Finally, the assertiveness of the patient demand is also influenced by the way they experience their relationship with the prescribing practitioner (see below: [Strength of ambulatory practitioner independence in relation to patients]) (Figure 33).

A second key concept is [Patient understanding of effects of AB use]. This is also a health literacy-related factor that is influenced by the professional's competence to clearly communicate with patients about the effects of antibiotics [Ambulatory practitioner ability to communicate with patients on antibiotic effects] and by the [Time available for a consultation]. Both factors are often seen to compromise patients' understanding. Limited understanding of the effects of antibiotics by patients is seen to negatively affect [Patient treatment compliance] and the tendency for [Patient antibiotic self-medication]. Another factor that contributes to patient's tendency to auto-medicate is the fact that prescribers do not have the [Ability to adjust packaging size to treatment] as currently not all AB package sizes

correspond to the dose and duration mentioned in the guidelines. As a consequence, there are left-overs which can be used in another occasion (where they may not be indicated) or even transferred to family members and friends. (Note: for more information on the issue of the mismatch between AB pack size and guidelines for their use leading to self-medication, the reader is referred to section 8.2).

A third key concept is the [Strength of ambulatory practitioner independence in relation to patients]. A strongly independent practitioner will be able to resist patient demand for antibiotics. Practitioners' natural authority, associated with expertise, has seen steady erosion in recent times [Practitioner authority as perceived by patients]. This is seen to negatively affect their strength of independence (Figure 33).

Furthermore, strength of independence is positively influenced by the [Available time for a consultation] and by the [Personal character of the relationship between patient and AP]. Also the practitioner's personal characteristics will play a role. A more naturally self-confident practitioner will be able to take a more independent position vis-à-vis a patient [Self-confidence of ambulatory practitioner] (Figure 33).

This cluster also includes a significant number of factors that connect directly with the core factor [Prudence of antibiotics prescription of humans].

- The [Propensity of APs to avoid short-term patient risk] is seen to be a key factor that explains practitioners' prescription behaviour. This tendency for risk avoidance will be more pronounced when practitioners are on call [Emergence visits in ambulatory and hospital care] and do not have [Access to patients' medication history] (Figure 33).
- Another important factor that feeds directly into the [Prudence of AB prescription for humans] is the [Frequency of consultation]. A higher number of consultations naturally leads to more prescription opportunities. In Belgium, employees' obligation to show a doctor's certificate in case of sick leave increases the number of consultations [Obligation of medical doctor certificate for one-day sick leave] (Figure 33).

- In addition, in Belgium patients can freely choose their ambulatory practitioner. Patients' likelihood to switch practitioner to seek a second opinion (and a practitioner who is willing to prescribe antibiotics) is seen to negatively influence the prudence of practitioners' prescription behaviour [*Likelihood of antibiotic prescription by other ambulatory practitioners*] (Figure 33).
- [Access to and correct use of rapid diagnostic aids] positively influences ambulatory practitioners' prudence of prescription behaviour (Figure 33).
A clear [*Handover between hospital and ambulatory practitioners*] also contributes to the latter's prudence of prescription behaviour. Letters accompanying patients at hospital discharge need to clearly state what types of antibiotics have been used and for how long (Figure 33).

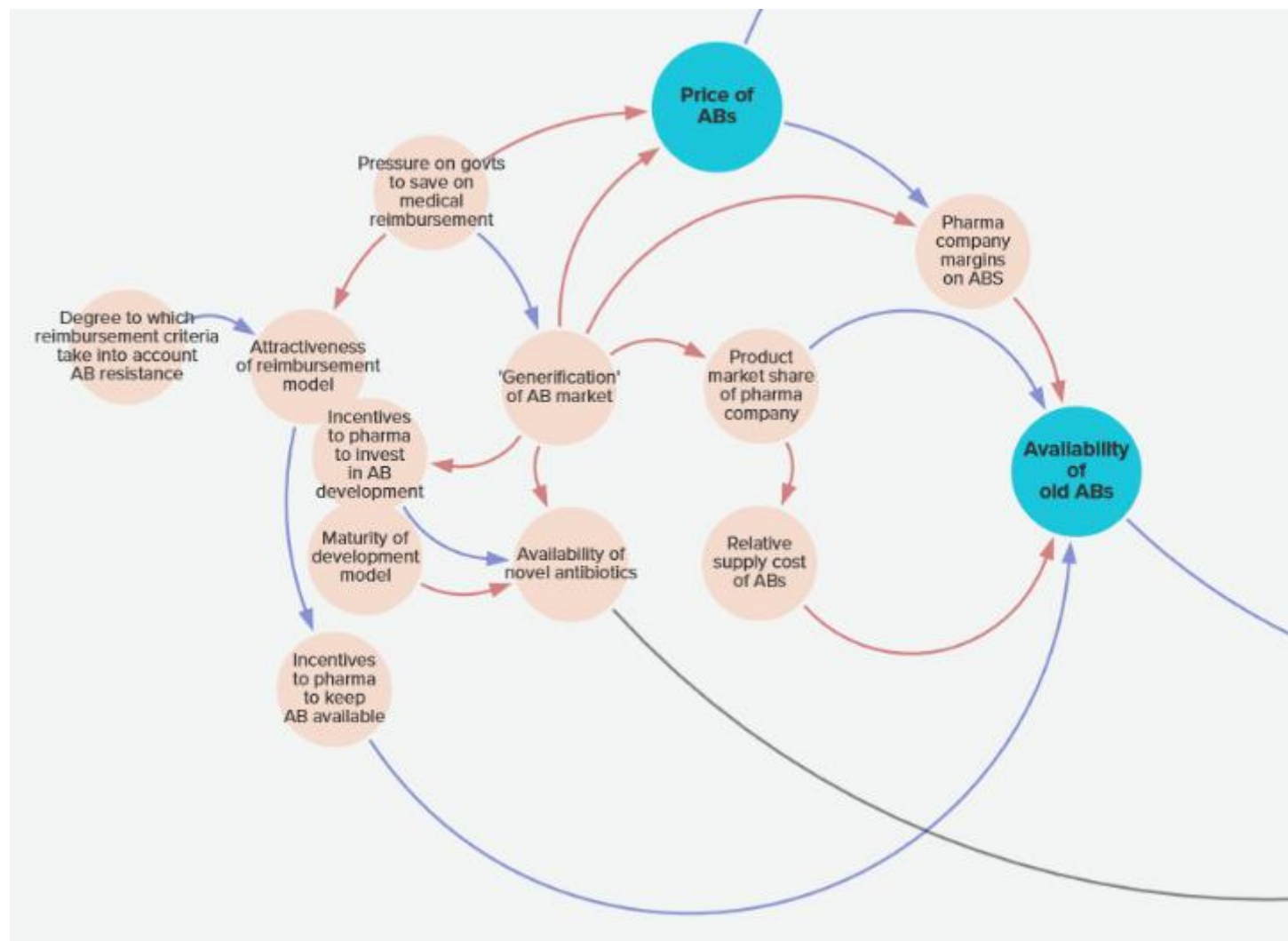


Cluster: Market of antibiotics

The first key concept (blue circle) in this cluster is the [*Price of antibiotics*]. The market of antibiotic drugs is dominantly served by manufacturers of generic drugs. This is the result of market dynamics surrounding mature, off-patent drugs [*Maturity of development model*] [*'Generification' of antibiotic market*] and the [*Pressure on government to save on medical reimbursement*]. Generification depresses prices of antibiotics, eroding pharma company margins on antibiotics [*Pharma companies' margins on antibiotics*]. Hence large volumes are important to justify presence in the market [*Product market share of pharma companies*]. Usually generic manufacturers do not invest in the development of novel products. This falls to innovation-driven companies. However, given prevailing market dynamics, there are few [*Incentives to pharma companies to invest in the development of antibiotics*]. Hence, there is a dearth of novel antibiotics available on the market [*Availability of novel antibiotics*]. A key factor to incentivise innovation-driven pharma companies to develop new drugs and to keep existing antibiotics in the market is the [*Attractiveness of the reimbursement model*] in vogue in a country. In Belgium, pharma companies seem to suggest that the reimbursement model is insufficiently attractive (Figure 34).

A second key concept is the [*Availability of old antibiotic*]. This ties into the market dynamics related to the price of antibiotics described above. Furthermore, an important factor that determines whether generic manufacturers keep existing antibiotics in the market is the [*Relative supply cost of antibiotics*]. An increasing relative cost – as a result of low margins and low volumes combined with high cost of handling – will lead them to withdraw older drugs that are potentially still very useful [*Availability of old antibiotics*]. In Belgium, practitioners complain about the unavailability of older antibiotics, which pushes prescribers towards (less appropriate) third or fourth generation molecules, which compromises prudence of prescription (Figure 34).

Figure 34 – Market of antibiotics





Cluster: Veterinary sector autoregulation

The core concepts in this cluster are [*Effectiveness of sector's autoregulation*] and [*Strength of historical recommendations for use of antibiotics*]. In moving towards increasingly prudent use of antibiotics the veterinary sector wishes to engage in active auto-regulation rather than to leave the initiative to the regulator. Initiatives are coordinated by AMCRA, the Belgian Centre of Expertise on Antimicrobial Consumption and Resistance in Animals, in which all stakeholders are represented (see section 3.4.3) (Figure 35).

- The animal sector has been afflicted by a prescription culture driven by economic motives [*Strength of historical recommendations for use of antibiotics*], [*Antibiotic-related interest of veterinarians*]. Hence, auto-regulation is a considerable challenge (Figure 35).
- The success of AMCRA clearly hinges on its [*Ability AMCRA to federate relevant actors*] (Figure 35), [*Farmer's organisation support for antibiotic policy*] and [*Government support for prudent AB use*] (see cluster: Farmers, Figure 36) reinforce the effectiveness of the sector's autoregulation. Farmer's organisations have been co-founders of the centre of expertise. AMCRA's strategic objectives were adopted by the federal government. Auto-regulation has become co-regulation in practice. Hence, the [*Enforceability of regulation of veterinary antibiotic use*] (see cluster: veterinary sector regulation, Figure 40) will support auto-regulation effectiveness.
- In the pig sector feed companies play an important role. It is a sector that is progressively intensifying and capitalising on economies of scale. Hence the [*Willingness of feed companies to support antibiotic auto-regulation*] (see cluster: livestock business model, Figure 38) is a determinant of the [*Effectiveness of sector's autoregulation*]. Relying on vets' compliance to prescribe [*Vets' receptiveness to antibiotic prescription guidelines*] (see cluster: guidelines, Figure 31) pig farmers used to rely to a significant extent on medicated feed [*Attractiveness to feed companies to produce medicated feed*] (see cluster: livestock business model, Figure 38) because of the many advantages associated, including the [*Antibiotic effect as growth promotor*] (see cluster: livestock business model, Figure 38). However, the climate around antibiotic use in the animal sector is changing and significant [*Investments (are) needed to dose antibiotic feed with antibiotics*] (see cluster: livestock business model, Figure 38). As a result, feed companies may become potent agents of change for more prudent use of antibiotics.
- Partly, AMCRA deals with the same challenges as BAPCOC in the human sector. The organisation requires [*Access to funding for scientific and administrative coordination*]. Its sensitisation efforts need to be underpinned by [*Visibility of AMCRA*], [*Consistency of messaging*] and [*Visibility of prevention campaigns*] (Figure 35).
- Effective autoregulation hinges on the availability of good quality and granular consumption data [*Granularity of consumption data*], sound registration of on-farm antibiotic use [*Effectiveness of AB registration system*] (see cluster: veterinary sector regulation, Figure 40) and effective sectorial benchmarks [*Effectiveness of sectorial benchmark*]. As a result one of the continuing priorities of AMCRA is to invest in the further development of a potent data collection system. However, this requires the collaboration of human operators, notably veterinarians and farmers. Considering the additional registration workload, stakeholders surmise that [*Financial compensation for the administrative impact of monitoring*] would increase the quality of the data gathered and hence the effectiveness of auto-regulation (Figure 35).
- The presence of pharmaceutical companies in AMCRA's Board has been a reason for suspicion in some corners of the stakeholder field. Pharmaceutical companies have been known to incentivise the use of antibiotics out of commercial motives [*Incentives from antibiotics producers*] which has contributed to [*Strength of historical recommendations for use of antibiotics*]. Hence the role of pharma companies in AMCRA may undermine the effectiveness of the sector's auto-regulation. AMCRA defends their presence because of their expertise and the fact that ultimately the strategic objectives of sector and pharma companies are aligned (Figure 35).



Figure 35 – Veterinary sector autoregulation





Cluster: Farmers

The key concept here is [*Farmers' receptiveness to guidelines for prudent antibiotic use*]. This is influenced by a number of factors that relate to farmers' education and expertise and their position as an entrepreneur (Figure 36).

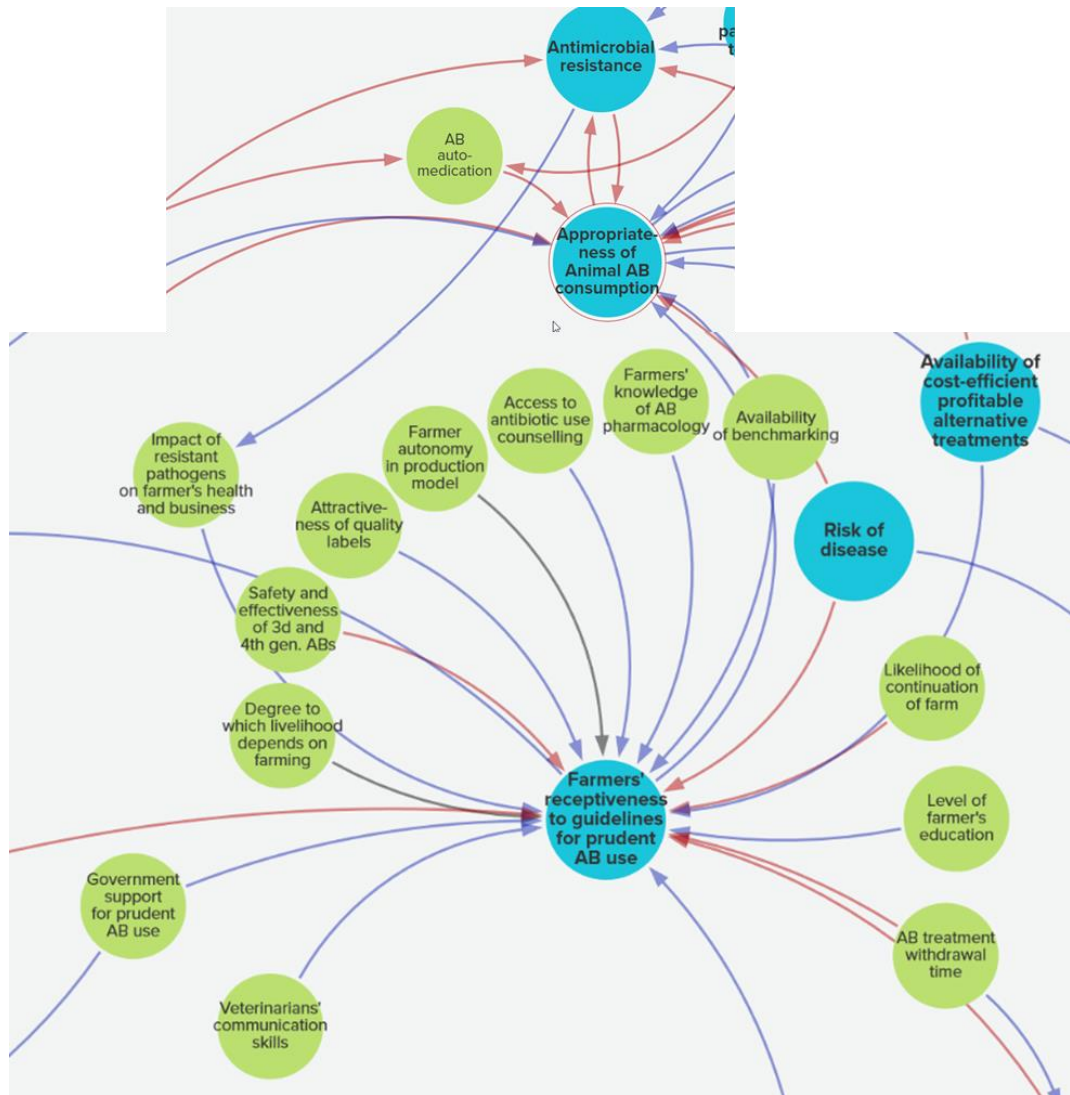
- Farmers are entrepreneurs who have to engage in risky investments to make a living. The [*Risk of disease*] is always present in intensive animal production environments. Hence, if guidelines for prudent antibiotic use are perceived to increase the risk for disease and hence potentially raise the [*Pressure on profitability*] (see cluster: livestock business model, Figure 38) it will make them shirk from guidelines. Ease of use and perceived effectiveness are powerful inducers to antibiotic use. The availability of later-generation antibiotics that are considered safe and effective certainly makes it harder to persuade farmers not to use them [*Safety and effectiveness of 3d and 4th generation antibiotics*]. Only the [*Availability of cost-efficient, profitable alternative treatments*] may provide a counterweight to these beliefs. Alternatives generally exist (for instance in the combination of vaccination with generally strict health and safety management on the farm) but farmers will not always be receptive to these alternatives (Figure 36).
- Older farmers who are looking forward to their retirement and/or do not have a successor will be more reluctant to adopt new guidelines for prudent antibiotic use and the above described alternatives [*Likelihood of continuation of farm*]. Part-time farmers may or may not be more receptive to guidelines [*Degree to which livelihood depends on farming*] (Figure 36).
- Another business-related factor is the [*Attractiveness of quality labels*] used in the production and distribution of animal (meat and dairy) products. Labels may lead to a premium in the market. The specifications associated to these labels could be powerful levers to incentivise farmers to adopt guidelines for prudent use of antibiotics. Data gathered by label managers may help farmers to benchmark themselves vis-à-vis their peers [*Availability of benchmarking*]. Related to this is the role of retailers, who bring farmers' products to the final customer and wield a significant influence over the upstream food production chain. [*Pressure of retailers to reduce antibiotic use*] (see cluster: livestock business model, Figure 38) could offer important incentives for farmers to adopt more prudent antibiotic use. However, the problem seems to be that consumers are unwilling to pay a premium for meat or dairy products that have been produced with particular regard to prudent antibiotic use (Figure 36).
- A (pig) farm may be part of a larger, vertically integrated entity owned by a feed company. In that case the farmer has less autonomy in deciding production parameters such as use of antibiotics [*Farmer autonomy in production model*]. Depending on the feed company's position vis-à-vis the use of medicated feeds this may increase or decrease a farmer's receptiveness to guidelines for antibiotic use. A similar reasoning applies to the [*Role and authority of veterinarians' in the production model*] (see cluster: veterinarians' AB practices, Figure 39). When they are employed by feed companies they will obviously have to adjust their prescription behaviour to the company strategy.
- Farmers are also human beings who due to continuous proximity to animals may experience adverse effects on their health [*Impact of resistant pathogens on farmer's health and business*]. This will positively influence their receptiveness to guidelines (Figure 36).
- Mostly, [*Farmers' knowledge of antibiotic pharmacology*] is low. This makes it harder to convince them to adopt guidelines for prudent antibiotic use. The [*Level of farmer's education*] also plays into this. Also, guidelines for antibiotic use have to be easily accessible for farmers [*Access to antibiotic prescription guidelines*] (see cluster: AB guidelines, Figure 31). One way to alleviate the impact of these knowledge gaps is provide farmers with [*Access to antibiotic use counselling*]. Stakeholders think that external counsellors or coaches that collaborate with farmers over longer periods of time can have a significant impact on their receptiveness to guidelines. The veterinarian is another key figure. [*Veterinarians' communication skills*] are an important factor in influencing farmers' receptiveness (Figure 36).



- Finally also the presence of [*Government support for prudent antibiotic use*] may be a positive influence on farmer's willingness to adopt guidelines as is the [*Enforceability regulation of veterinary antibiotic use*] (see cluster: veterinary sector regulation, Figure 40).
- [*AB treatment withdrawal time*] reflects the amount of time necessary for an animal to metabolize an administered product and the amount of time necessary for the product concentration level in the tissues to decrease to a safe, acceptable level before the animal can be slaughtered. This is specific for each antibiotic. Obeying withdrawal time instructions imposes a financial burden on the farmer's business arising from an increased timespan of livestock housing. In addition, disease outbreak [*Risk of disease*] during the withdrawal time will further increase the [*Pressure on profitability*] (see cluster: livestock business model, Figure 38). This reasoning reveals that an increased antibiotic treatment withdrawal time may lead to a decreased [*Farmer's receptiveness to guidelines for prudent AB use*] (Figure 36).



Figure 36 – Farmers





Cluster: Livestock business model

The key concepts in this cluster are [*Pressure on profitability*], [*Risk of disease*], and [*Availability of cost-efficient, profitable alternative treatments*] (Figure 37, Figure 38).

- Farmers operate in global and very competitive market place, putting [*Margins per unit of livestock*] under pressure. Declining margins increase the [*Pressure on profitability*]. Farmers may seek alternative sources of income to offset this trend. They may seek to capture value from waste streams of the production process (for instance turning biomass into energy) [*Ability to capture value from waste streams*]. They may offer premium products to consumers willing to pay more. Meat or dairy products from animals raised on prudent antibiotic regimes could be considered such a niche category. However, stakeholders point out that in practice [*Consumers' willingness to pay premium for antibiotic free food*] is low (Figure 37, Figure 38).
- Low margins push producers towards more intensive production methods. A high [*Intensity of livestock production*], particularly of a highly homogenous animal population [*Heterogeneity of livestock production*] engenders [*Risk of disease*] and has negative [*Environmental impacts*]. Farmers try to mitigate this risk of disease through the use of antibiotics [*Appropriateness of animal antibiotic consumption*] (see cluster: farmers, Figure 36), including the preventive use of medicinated animal feeds [*Preventative animal consumption of medicinated feed*] (see cluster: veterinarians' AB prescriptions practices, Figure 39). Particularly the low [*Cost of antibiotics*] and the [*Ease of application of antibiotics*] are strong incentives to use these products given the strong [*Pressure on profitability*]. A factor that

reduces the attractiveness of antibiotics is the withdrawal time required to reduce the concentrations of antibiotics to levels considered safe for human consumption [*Antibiotic treatment withdrawal time*] (see cluster: farmers, Figure 36) (Figure 37, Figure 38).

- In mitigating risk for disease and given the increasingly obvious impact of antibiotics on antimicrobial resistance, livestock producers may seek to rely on alternative treatments. However, given the small margins in livestock production it is, from a business point of view, crucial that these alternative treatments are as cost-efficient and profitable as the use of antibiotics [*Availability of cost-efficient, profitable alternative treatments*]. Stakeholders surmise that in (the perceived) absence of these alternatives, producers may resort to euthanasia rather than treatment of animals at risk [*Animal health and welfare*]. Another challenge may reside in the environmental burden related to alternative treatments. For instance, use of zinc oxide in the piglet feed (banned in the EU since 2017, with a phasing out of 5 years) has led to severe pressure on soil quality [*Environmental impacts*] (Figure 37, Figure 38).
- Maintaining [*Animal health and welfare*] in intensive production settings is to a significant extent a matter of a rigorous on-farm health and safety approach. Clean and well ventilated stables are a key factor in reducing the [*Risk of disease*]. This requires [*Investments in infrastructure*]. Whether farmers are willing to commit to these investments is generally a matter of [*Quality of stockmanship*] which is influenced by the [*Level of farmer's education*] (see cluster: farmers, Figure 36) and by the [*Farmer's perception of the impact of biosecurity measures*]. Other factors may enter the investment calculus, for instance the [*Likelihood of continuation of the farm*] (see cluster: farmers, Figure 36) (Figure 37, Figure 38).



Figure 37 – Livestock business model 1

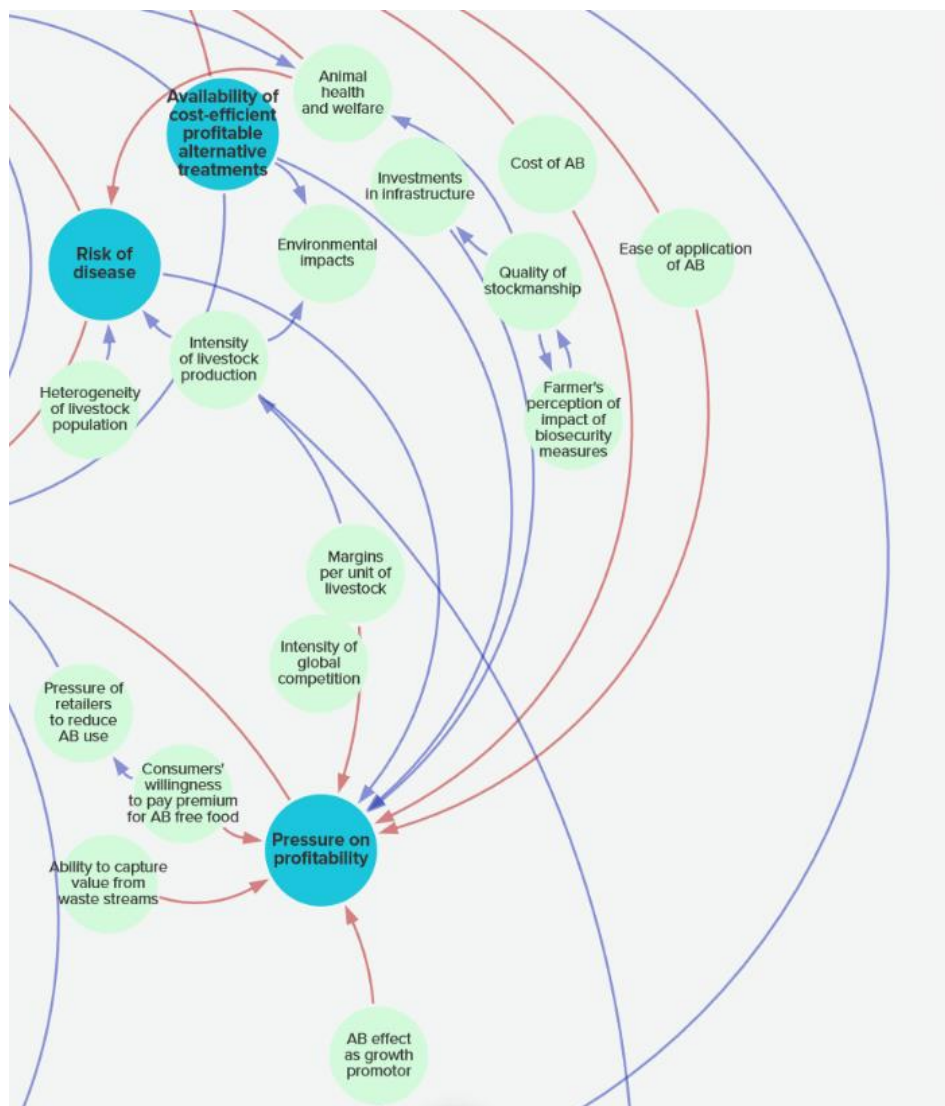
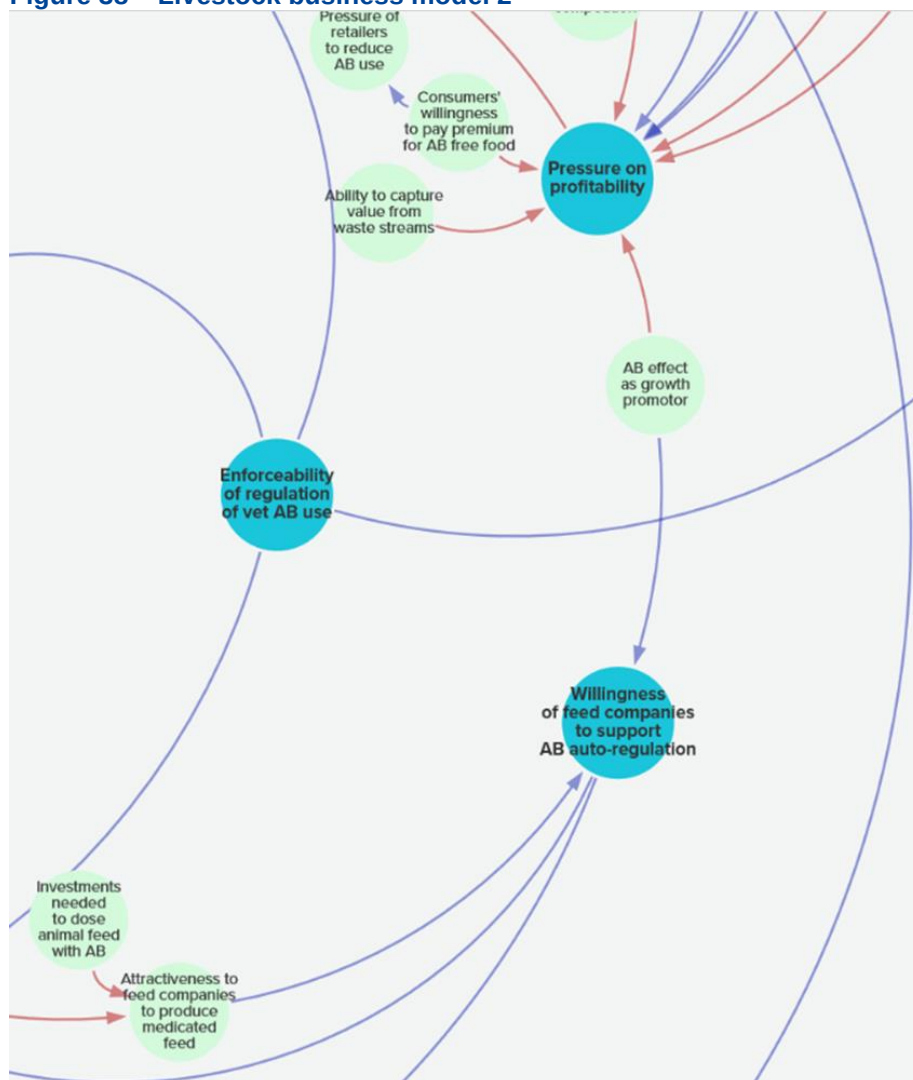




Figure 38 – Livestock business model 2





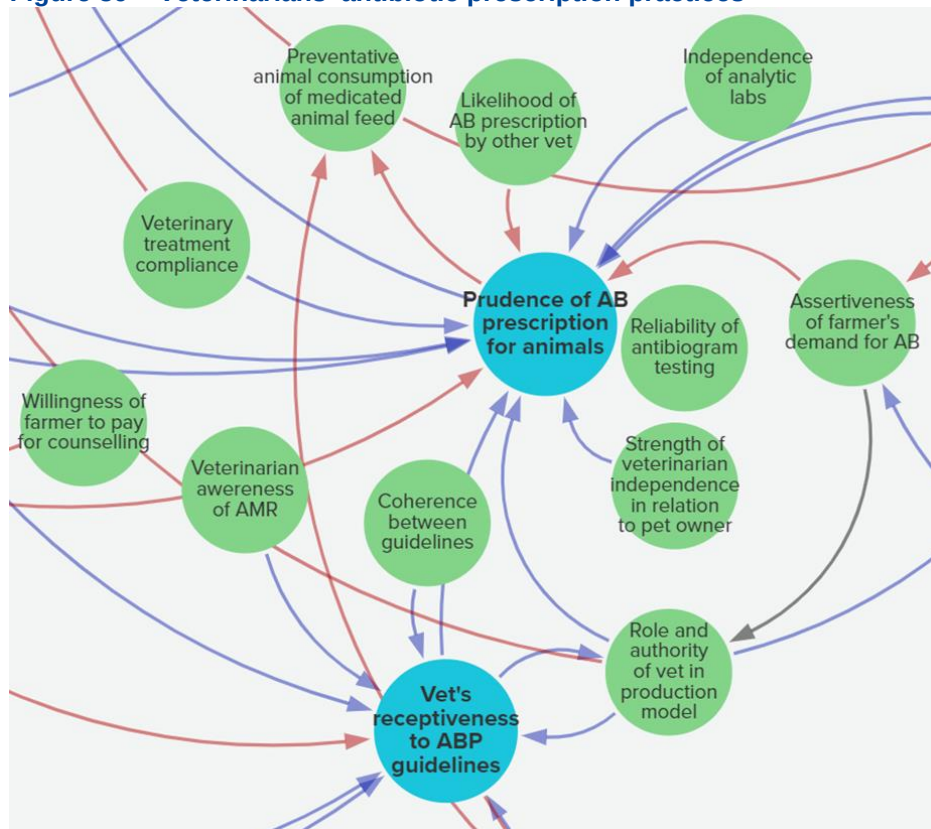
Cluster: Veterinarians' AB prescriptions practices

The key concepts in this cluster are [*Prudence of veterinary antibiotic prescription*] and [*Antibiotic-related economic interest of veterinarians*] (see cluster: veterinary sector autoregulation, Figure 35). In the discussion of this cluster also concepts related to the [*Vet's receptiveness to antibiotic prescription guidelines*] are included (Figure 39).

- Veterinarians are key actors in the move towards prudent use of antibiotics in the animal sector as they have prescribing rights. Their decision-making regarding antibiotic use is influenced by psychological, economic and therapeutic factors.
- In relationship to farmers, their clients, vets need to be able to take a psychologically independent stance. This may prove to be challenging given the routinely high [*Assertiveness of farmers' demand for antibiotics*] and the [*Likelihood of antibiotic prescription by other vets*]. Psychological pressure to prescribe is likely even more pertinent in relationship with pet owners, given owners' strong bond with their animals [*Strength of veterinarian independence in relation to pet owner*] (Figure 39).
- The animal sector has historically been afflicted by a prescription culture driven by economic motives. Veterinarians' revenue may be boosted by the sales of pharmaceutical products, including antibiotics. Hence, the [*antibiotic-related economic interest of veterinarians*] (see cluster: AB guidelines, Figure 38) may compromise their [*Prudence of antibiotic prescription*]. The attractiveness of this business model can to an extent be explained by the observation that the [*Farmers' willingness to pay for counselling*] is often low. Key is also the [*Role and authority of the vet in the production model*]. Particularly in Flanders there has been a trend in vertical integration of animal production. This has led to streamlining and standardisation of production rounds in which the vet has less autonomy and follows prescription guidelines from the mother feed company. Veterinarians may also have a contract with farms for company guidance. In that case they develop a longer term relationship which may offer opportunities for more sensitive and prudent use of antibiotics. On the other hand, there are also risks regarding [*Veterinary*

treatment compliance] as vets may put larger volumes of antibiotics at the discretion of the farmer, making it harder to assess their appropriate use. Hence the connection between [*Role and authority of the vet in the production model*] and [*Antibiotic self-medication*] (see cluster: Farmers, Figure 36). [*Ability to adjust packaging size to treatment*] (see cluster: AP & patient relationship, Figure 33) also feeds into [*Antibiotic self-medication*] (see cluster: Farmers, Figure 36).

- [*Access to antibiotic prescription guidelines*] (see cluster: AB guidelines, Figure 38) provides veterinarians with therapeutic support for responsible use of antibiotics. AMCRA is publishing and updating these guidelines on a regular basis [*Visibility of antibiotic prescription guidelines*] (see cluster: AB guidelines, Figure 38). [*Veterinarian's receptiveness to antibiotic prescription guidelines*] is influenced by their Awareness of [*Antimicrobial resistance*] (see cluster: Farmers, Figure 36) issues, the [*Coherence between guidelines*] and the [*Perceived legitimacy of antibiotic prescription guidelines*] (see cluster: AB guidelines, Figure 38). Stakeholders interviewed have pointed out that veterinarians have been insufficiently consulted in the development of guidelines. Also they note inconsistencies between recommendations and assessments made regarding the list of critically important antibiotics by international bodies such as the World Health Organisation (regarding use of antibiotics for human health) and the World Organisation for Animal Health [*International consensus on list of critically important antibiotics*], [*International coherence of antibiotic guidelines*] (see cluster: AB guidelines, Figure 38). These inconsistencies are unresolved in the guidelines at national level. Finally, the legitimacy of AMCRA-published guidelines has been criticised because of the [*Involvement of the pharmaceutical sector in guideline development*] (see cluster: AB guidelines, Figure 38). AMCRA defends this approach by pointing out that pharma companies have significant expertise that adds to the quality of the guidelines.
- Vets may also seek additional confirmation for prescribing antibiotics via antibiotic sensitivity testing [*Reliability of antibiogram testing*]. Key requirement is that the results produced by analytic labs are trustworthy [*Independence of analytic labs*] (Figure 39).

**Figure 39 – Veterinarians' antibiotic prescription practices**



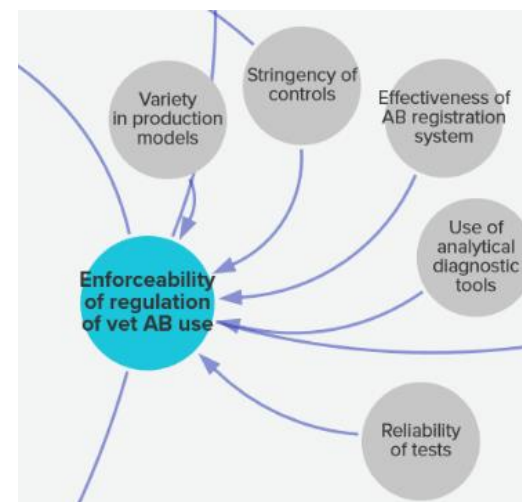
Cluster: Veterinary sector regulation

The key concept is [*Enforceability of regulation of veterinary antibiotic use*]. This cluster deals with the hurdles to effective and enforceable regulation in the animal sector. There are five concepts feeding into it:

- The [*Variety in production models*] across the sector, not only across different animal subsectors but also within a given subsector. Stakeholders note that each farm is different, and that it is difficult to develop one-size-fits-all regulation (Figure 40).
- On-site controls of farms take time and resources. As a result controls may be too infrequent to pose much of a perceived risk to producers [*Stringency of controls*]. The analysis of samples needs to rely on sensitive and accurate test methods. The developments of these tests for different subsectors is evolving [*Reliability of tests*] (Figure 40).
- The law now requires the use of third and fourth generation antibiotics to be accompanied by an antibiogram [*Use of analytic diagnostic tools*]. The presence of an antibiogram is easy to verify and increases the enforceability of the regulation of the use of these late-generation antibiotics.
- Farmers and vets are required to register the use of antibiotics on their premises. The online SANITEL-MED application facilitates the registration and makes the data easy to consult [*Effectiveness of AB registration system*] (Figure 40).

The key concept [*Enforceability of regulation of veterinary antibiotic use*] feeds into four other key concepts in different clusters: [*Farmers' receptiveness to guidelines for prudent antibiotic use*] (see cluster: Farmers, Figure 36), [*Prudence of veterinary antibiotic prescription*] (see cluster: Veterinarians AB prescriptions practices, Figure 39), [*Effectiveness of sector's autoregulation*] (see cluster: Veterinary sector autoregulation, Figure 35), and [*Appropriateness of animal antibiotic consumption*] (see cluster: Farmers, Figure 36) (Figure 40).

Figure 40 – Veterinary sector regulation



7.5.3 Assessment of the scope of the systems map

To assess the scope of the map, a comparison was made with the determinants of antibiotic use mentioned in the literature (see Chapter 5). It is important to note that, the literature reviews on determinants did not cover the effectiveness of interventions (which are covered by chapter 6), while concepts related to interventions (and their effectiveness) are included in the map. This would be a first factor for discrepancies between the two lists.

Table 58, Table 59 and Table 60 in Appendix 5.3 list determinants of **veterinary** antibiotic use identified from the literature and matches those with related concepts from the systems map. Concepts do not have to exactly mirror determinants but have to reflect an issue that is sufficiently similar. The aim of the matching is to assess whether and to what extent the scope of the systems map reflects the ambit of research into determinants of antibiotic use.



The matching indicates that there is good overlap between the determinants discussed in the literature and the concepts included in the map. Determinants cover aspects of almost all clusters in the map. The only cluster of concepts that is not reflected by the determinants relates to veterinary sector auto-regulation, which is a specifically Belgian approach to a sector-wide process of change towards more responsible use of antibiotics. Conversely, the determinants that are not matched by concepts in the map fall into two categories: animal and therapy-specific determinants (reflected in determinants such as 'animal age', 'animal body weight', 'animal species and associated behaviour', 'previous clinical history of the animal', 'duration of antibiotic therapy') and professional ethos and expertise of veterinarians (reflected in determinants such as 'years of experience', 'personal preference of AB', 'knowledge of non-infectious diseases', 'attitudes, risk perception and aversion', 'confidence in own knowledge regarding disease prevention'). In the human part of the systems map the latter category is more prominently represented.

As regards the **human** part of the systems map, the matching of determinants identified in the literature (related to the Belgian situation) and the concepts included in the map is presented in Table 58 (Appendix 5.3). The table illustrates that for the human part of the systems map there is a good match between concepts and determinants related to prescriber, health care system and patient.

On the whole the comparison gives confidence that the scope of the systems map reflects the breadth of the research on determinants for both veterinary and human sectors.

7.5.4 Stakeholders' suggestions to improve antibiotic policy, prescription and use

In this section the results of the second stakeholder workshop are reported (see section 7.4.6). First the results of the deliberations in each subgroup (veterinary, human ambulatory, human hospital) are reported in tabular format (Table 50, Table 49 and Table 48). The table lists the suggested improvements for antibiotics policy, prescription and use. Suggestions are grouped in the clusters proposed by the subgroups. Also the number of 'votes' gathered in the prioritisation round are listed in a separate column. Suggestions are listed in decreasing order of weight in terms of number of votes. In some cases additional observations or comments from project team facilitators are included. In the following paragraphs the comments made by subgroup representatives in sharing the results of the group discussion are summarised. The final section includes key points from the concluding plenary discussion.



7.5.4.1 Output of the ambulatory care subgroup

Table 48 – Output of the ambulatory care subgroup

Cluster	Suggestions	Number of votes in the plenary	Match with the systems map
Electronic prescription (e-prescription)	<ul style="list-style-type: none"> Add the indication/diagnosis in the field required for the electronic prescription. This could trigger a warning if the AB prescribed is not in line with the diagnosis (both the need for AB and the choice of the AB). Automated link to BAPCOC guidelines and others, related to the diagnosis, through electronic prescription (as a Computerized Decision Support System). Provide real-time access to individual feedback for GPs/doctors (on prescriptions) and to benchmarking (based on other GPs), and link it to positive reward/incentive programme related to accreditation. Integrate regulation for AP prescription to the e- prescription, such as providing a link to criteria and necessary documents, e.g. for quinolone prescription (Chapter IV). 	11	<p>Use of electronic prescription</p> <p>Ability to impose restrictions on empirical prescription Practitioner access to antibiotic prescription guidelines; cross-therapeutic integration of guidelines.</p> <p>Information overload of medical practitioners (MPs)</p> <p>Incentives associated to individual prescription profiles. Financial incentives to AP to reduce AB prescription</p> <p>Possibility to have access to personalised, authoritative feedback on prescription behaviour; Use of electronic prescription system to collect antibiotic prescription data (incl. diagnosis).</p>
Health system organization	<ul style="list-style-type: none"> Replace fee-for service by capitation system and increase independence of the relationship GP-patient. Revise the sick leave system (for work and school) i.e. the need for a physician's certificate in the case of 1 or 2 days of sickness leave. A lot of patients with viral infections won't visit their physician anymore if they don't need a certificate and so this will decrease the pressure to prescribe unnecessary AB The price/co-payment for patients should be increased to improve responsibility of the patient / so that they become an involved partner, <i>no consensus about this proposal</i> Need for one single coherent authority responsible for antibiotic policy and guidance, across all levels of health authority, and more transparency 	10	<p>Impact of fee-for-service reimbursement.</p> <p>Strength of independence of ambulatory practitioner in relation to patient.</p> <p>Obligation for medical doctor certificate for one-day sick leave.</p> <p>Cost to patients of antibiotics.</p> <p>Effectiveness of intersectoral coordination.</p>



Cluster	Suggestions	Number of votes in the plenary	Match with the systems map
			Complexity of Belgium political landscape Continuity of AB policy; Transparency of intersectoral coordination
AB Stewardship for Ambulatory Care	<ul style="list-style-type: none"> • Install local antibiotic stewardship groups for ambulatory care (one team of GPs with more expertise in infectious diseases for a number of GP practices) to discuss local situation, possible interventions, and regular feedback. This could be initiators of change at a local level/hospital. This could also improve GPs self-confidence when prescribing antibiotic or not (mistakes are allowed) • Standardize the content and frequency of continuous education of GPs through LOK – GLEM/other at national level, and link this with feedback on prescription. • Ensure regular evaluation of these proposed measures. 	9	Quality and availability of information through LOKs – GLEMs; Possibility to receive feedback and discuss best practices with peers; Access to trusted sources of scientific expertise. Influence of senior peers Self-confidence of AP
Data and Evidence for AB use and AB resistance	Data for the individual level: <ul style="list-style-type: none"> • Provide to AP timely data and evidence on AB use and AB resistance. Provide ABR data based on community level strains (vs. hospital ABR) See e- prescription. • Improve the timeliness and comprehensiveness of the individual AB feed-back and link it to incentives (see e- prescription) • There should be only one source of guidelines for AB prescription for AP. Data at population level: <ul style="list-style-type: none"> • Improve the timeliness and comprehensiveness of the outcome measures to monitor AB use and ABR 	8	Availability of tailored epidemiological data; Possibility to have access to personalised, authoritative feedback on prescription behaviour. Pertinence of surveillance and consumption data; Access to an integrated set of indicators. Coherence amongst national guidelines. Visibility of AP guidelines Access to AP guidelines Incentives associated with individual prescription profile; Financial incentives to AP to reduce AB prescription



Cluster	Suggestions	Number of votes in the plenary	Match with the systems map
AB dosage	<ul style="list-style-type: none"> Authorize, implement and promote the delivery and reimbursement of antibiotics per unit, set up a targeted campaign to inform the population and elaborate a rapid monitoring and feedback system so that the impact can be followed up Make adequate package sizes available to patients, in accordance with the duration of treatment 	3	Ability to adjust packaging size to treatment.
Sensitization	<ul style="list-style-type: none"> Communicate better on the “why” message to the public, and include the link with the use in animal/human waste. Empower patients and apply “safety net” advice to favour more self-confidence in their ability to heal without AB. 	3	<p>Patient understanding of effects of antibiotics use.</p> <p>Degree to which patients trust own healing resources.</p>
Policy	<ul style="list-style-type: none"> Ensure a better coordination between different actors /stakeholders when a decision is being taken about AB (e.g. quinolones in Chapter IV): check the decision-making process on “new processes” with stakeholders before introducing them. Improve transparency on new policy and communicate it to all stakeholders (e.g. frustration about quinolones in Chapter IV). 	1	<p>Effectiveness of intersectoral coordination.</p> <p>Coherence of AB policy</p> <p>Complexity of Belgian political landscape</p>

AB: antibiotic(s); ABR: antibacterial resistance; AP: Ambulatory Practitioner; BAPCOC: Belgian Antibiotic Policy Coordination Committee; GP: general practitioner; LOK – GLEM: Lokale kwaliteitsgroep -Groupe local d'évaluation médicale.

Summary of the discussion

There were several suggestions for electronic prescription. One was to add the indication (diagnosis) in the electronic prescription system, which is currently not the case (yet), so that the reason for prescription is registered. The indication would allow to: 1. evaluate whether the antibiotics were justified for that indication (prudent use), and could trigger a warning if the antibiotic prescribed is not in line with the diagnosis (both the need for antibiotic and the choice of the antibiotic); 2. measure the rate of appropriate use of antibiotic - and not only the crude antibiotic use; 3. make an automatic link to the guidelines relevant to the indication; 4. integrate regulations on the GP prescription, e.g. if a GP wants to prescribe a quinolone, the authorisation and mandatory documents are automatically fed into the system. The electronic system could also be used to provide direct access and real time feedback to the individual GP, comparing his prescription behaviour with peer GPs from the same geographical area. This could also

lead directly to incentives (and financial sanctions) for (in-) appropriate prescription and create a positive attitude towards prescription of antibiotics by GPs. All this would happen in real time.

Further suggestions were linked to quality and timeliness of data and evidence for antibiotic use. Practitioners need to have access to recent data on local antibiotic use and antimicrobial resistance, but also to data on antibiotic resistance that are related to community-based antibiotic resistance, while most available ABR data are currently based on hospital strains (that usually have higher level of ABR). The timeliness of feedback should be improved on a general level, and be linked to incentives. And there should be just one source of guidelines, in order to avoid the current situation of having multiple references for treatment. When speaking about data on a population level, the group also proposes to improve the timeliness and comprehensiveness of the different outcome measures to monitor the antibiotic situation at national level.



There was also a (new) cluster that the group calls 'antibiotic stewardship for ambulatory care'. There were five suggestions: to create local antibiotic stewardship teams for ambulatory care - like in a hospital, but for a number of GP practices. GPs that are more specialized in infectious diseases could coach other GPs and increase their self-confidence when deciding on antibiotics prescription for their patient. The group also proposes to standardize continuous education in LOK – GLEM or other places, so that content and frequency would be more standardized in the entire country. And the group also advised to have continuous assessment and evaluation of those proposals.

The group also came forward with suggestions that targeted the broader organisation of the health care system. A provocative and maybe utopic proposal was to change the fee-for-service (that increases the risk of antibiotic prescription) for a capitation system, in which GPs are more independent of their patient demand. Another proposal would be to revise the actual system for sick and school leave, i.e. drop the request for a doctor's certificate for 1 or 2 days leave, because this way people get the chance to recover without seeing a GP, and by extension taking medication in case of small health problems. This would also change the relationship between patient and GP in terms of dependency. One person proposed to increase co-payment for AB by the patient to increase their sense of responsibility, but there was no consensus on that proposal as several members of the group were against it. Knowing that we have six ministers for health, it would be important to have one single (high level) authority responsible for antibiotic policy across all levels of health authority, which would be more transparent than the current system.

Four proposals related to antibiotics package size. Three concerned the introduction of an antibiotic 'per unit' prescription and delivery system and to change regulations and legislation and other barriers that are blocking such a system. It would also require good information campaigns of the population and the patients themselves, as well as good monitoring and evaluation of the measure. A fourth proposal, consisted not of a 'per unit' system, but at least an adequate package size that is more appropriate to the patient treatment.

This group reflected also on policy, proposing to have better coordination between different actors/stakeholders when a decision is being taken about antibiotics: when a decision is being taken about antibiotic (e.g. quinolones included in Chapter IV, see section 3.3.1), the decision-making process should involve all stakeholders. The transparency should also be improved on new policy and be communicated to all stakeholders.

Finally, there was also a cluster about sensitization, with two proposals: (i) to better communicate the "why" of the message on prudent antibiotic use, which is not that easy to explain clearly in AMR, and (ii) to empower patients to increase their self-confidence, including the use of "safety net" advises (see Chapter on Interventions), and decrease their psychological reliance on antibiotics.

Prioritisation: The cluster with highest number of votes (11, this is also the highest number across all three subgroups) includes the suggestions related to the leveraging of the electronic prescription system. This generates an information flow that can be most effective in influencing prescribing behaviour. Then follows another cluster with a very high number of votes (10) with proposals related to the organisation of the broader health care system. The next two cluster score 9 and 8 votes, respectively. They deal with suggestions that aim to create an environment where ambulatory practitioners receive timely and pertinent feedback on their prescription behaviour, have the opportunity to learn from peers and are offered pertinent and local epidemiological and surveillance data. The remaining clusters received a smaller number of votes.

Match with the systems map: The suggestions connected most markedly with concepts feeding into the key concept 'practitioner expertise regarding prudent AB use'. Other important concepts link directly to 'prudence of antibiotic prescription for humans'. There were few suggestions that relate to the cluster 'ambulatory practitionerrelationship'. Less prominent also are concepts belonging to the 'Policy' and 'Sensitization' clusters.

7.5.4.2 *Output of the hospital care subgroup***Table 49 – Output of the hospital care subgroup**

Cluster	Suggestions	Number of votes in the plenary	Match with the systems map
Responsibilize and incentivize hospital management to support AB steward activities	<ul style="list-style-type: none"> The antimicrobial stewardship teams need to be supported by the hospital's direction Hospitals need quality indicators to measure the quality of antibiotic prescribing and outcome of the patients. There should be an incentive, i.e. pay for performance, to sensitise hospital management. But also, the results should be made available to the public. Rationale: in this way administrators will be aware that they should invest in support (human and technological) 	9	<p>Support from hospital management.</p> <p>Coupling of hospital financing to antibiotic prescription-related quality indicators; Financial incentives based on benchmarking of prescription behaviour; Level of IT support; Funding of in-hospital antibiotic stewardship teams</p>
Set targets for quality of prescribing; quantity of prescribing; reduction of the healthcare associated infections	<ul style="list-style-type: none"> Set targets for quality of prescribing; quantity of prescribing (volume of AB use) (involve AB stewardship teams) Set targets for the reduction of <ul style="list-style-type: none"> Healthcare associated infections Antimicrobial use 	6	Reliability and timeliness of interhospital benchmarking; Reliability and timeliness of individual hospital prescription data
Provide adequate operational support of AB steward teams	<ul style="list-style-type: none"> Increase support of AB stewardship teams by BAPCOC in terms of concrete projects and quality improvement initiatives, e.g. audits; implementation tools Increase presence of experts in infectiology in the wards, so that surgeons do not have to deal anymore with ABs, only with surgery Increase hospital pharmacy efforts targeted on AB use, cf. ward physicians 	6	<p>Support of BAPCOC working group; Authority of AB stewardship teams; collaboration between AB stewardship teams</p> <p>Receptiveness of clinicians to direct interference by infectiologist.</p>
Provide good quality and timely data to AB stewardship teams, prescribers, management, infection prevention teams	<ul style="list-style-type: none"> Invest in IT infrastructure in order to optimize e-prescription so as to facilitate data collection on AB prescription and use Include benchmarking per diagnosis in the surveillance of antimicrobial consumption Find solutions for the delay of feedback in the surveillance of antimicrobial consumption; this may be solved with e-prescriptions if they include diagnosis 	5	<p>Use of electronic prescription system to collect antibiotic prescription data, incl. diagnosis; Level of in-house IT support.</p> <p>Reliability and timeliness of individual prescription data; Access to lab results.</p>



Cluster	Suggestions	Number of votes in the plenary	Match with the systems map
	<ul style="list-style-type: none"> Synthesize all information ever collected from hospitals (survey, audit ...) and make an overall report per hospital including their strengths and weaknesses, points for actions at hospital level (<i>note: there was little support from the group regarding this suggestion</i>) 		Reliability and timeliness of interhospital benchmarking; Reliability and timeliness of individual hospital prescription data.
Provide adequate financial support of AB stewardship teams	<ul style="list-style-type: none"> Each hospital should receive financial support to have a multidisciplinary infection team on the floor (i.e. working in or having close contact with the different wards), which should document their interventions. 	4	Approval of infectiology and medical microbiology as medical speciality; Receptiveness of clinicians to direct interference by infectiologist; Authority of AB stewardship teams.
Improve a coherent set of national guidelines and enforce implementation	<ul style="list-style-type: none"> Avoid conflicts between guidelines. Education of physicians, pharmacists: national guidelines are electronically available for the treatment of infectious diseases. In order to implement these guidelines, universities should use these guidelines in the education of physicians and pharmacists. These guidelines should be used as guidelines in the hospitals, possibly with some adaptations to the local situation Create barriers for the use of certain ABs in hospitals, e.g. Moxifloxacin (cf. ambulatory care) Avoid combinations of antibiotics (unless authorized as combination) 	1	<p>Coherence amongst national guidelines; Quality of national guidelines.</p> <p>Practitioner access to guidelines; Practitioner receptiveness to guidelines for prudent antibiotic use; Quality of academic training; Clinical interest of antibiotics to medical practitioners.</p>
Change business model/duration of AB patents	<ul style="list-style-type: none"> Change business model/duration of AB-patents 	0	Availability of novel antibiotics; Availability of old antibiotics; Incentives to pharm to invest in antibiotic development.
Develop a more integrated and effective sensitization campaign machinery	<ul style="list-style-type: none"> To repeat 4 times a year strong messages about prudence of AB prescription (cf. Coca Cola strategy) Improvement & development of sensitization materials targeting different actors and make these materials available more than one time a year. Continuous sensitization in hospitals. 	0	<p>Persistence of sensitisation campaigns.</p> <p>Persistence of sensitisation campaigns; Timeliness of sensitisation campaigns.</p>
Empower prescribers	<ul style="list-style-type: none"> Develop smart clinical decision support systems (CDSS) for prescribers taking into account the indication, lab results, patient-specific factors, other medication 	0	Cross-therapeutic integration of guidelines.



Cluster	Suggestions	Number of votes in the plenary	Match with the systems map
	<ul style="list-style-type: none"> Implement system of selective reporting of antibiotic susceptibility (involve labs) Bring together the expertise of the microbiologic labs in order to look for and implement diagnostic tools to obtain lab results in a faster way Optimize the information flow on AB use to the medical doctors (in order to avoid burden of information) and measure the implementation of BAPCOC guidelines (get feedback from the field) 		<p>Access to lab results.</p> <p>Information overload of medical practitioners; Level of in-house IT support.</p>

AB: antibiotic(s); BAPCOC; Belgian Antibiotic Policy Coordination Committee; CDSS: clinical decision support systems, IT: information technology

Summary of the discussion

The sense was that the infrastructure within the hospital setting and the antibiotic stewardship teams is basically good. However, stewardship teams are not fully empowered. It was stressed that first of all stewardship teams are in need of more operational support. The move towards more prudent use of antibiotics ultimately needs to happen on the hospital floor. Two specific suggestions qua operational support were 1) to increase clinical pharmacy efforts targeted on antibiotic use 2) to make sure that also in smaller hospitals a physician would be present in wards at all times. For example in surgical wards it is very difficult to get the surgeon to be present at the ward to care for their hospitalized patients. Antibiotic use is certainly not a priority for them. There was also a suggestion to increase support of stewardship teams by BAPCOC in terms of concrete projects, quality improvement initiatives and other implementation tools.

Bottom-up operational support of stewardship teams need to be reinforced by top-down measures to lead to genuine behaviour change. Targets need to be set for the quality of prescribing, quantity of prescribing and reduction of health care associated infections. This would enable the implementation of pay-for-quality financing of hospitals. Hospital management need to be incentivised to energetically support stewardship activities. Financial incentives are inevitably part of the picture.

Empowerment also relates to the availability of adequate and timely data. There were several proposals to provide good quality and timely data to antibiotic stewardship teams, and more broadly to prescribers, hospital management, infection prevention teams and even to the general public.

A second element to support empowerment are coherent and enforceable guidelines. Barriers should be created regarding the use of certain antibiotics in hospitals, for example moxifloxacin. The prescription of combinations of antibiotics should be restricted to exceptional cases and the information provided in the guidelines should be adapted as such. Physicians and pharmacists also need to be trained in the proper use of guidelines. Sensitization campaigns – regarded as a third element – should be more integrated and more effective. This relies on continuity, coordination and integration amongst different actors and the different media.

Prioritisation by voting: The cluster with proposals to incentivise hospital management to support stewardship teams had a clear lead. Then followed a group of four clusters that scored somewhat similar (garnering 6, 6, 5 and 4 votes, respectively). They pointed to the need to strengthen operational, informational and financial support of stewardship teams. The remaining clusters received very few or no votes.



Match with the systems map: The proposals connected most markedly to the concepts feeding into the key concepts 'effectiveness of antibiotic stewardship teams in hospitals' and 'effectiveness of implementation of antibiotic prescription guidelines'. Less emphatic were the links to the clusters related to the effectiveness of sensitisation campaigns and the functioning of the antibiotics market (availability of both novel and old antibiotics).

7.5.4.3 Output of the veterinary subgroup

Table 50 – Output of the veterinary subgroup

Cluster	Suggestions	Nr of votes in the plenary	Related concepts in the systems map
Improve disease prevention and animal welfare	<u>Pharmaceuticals</u>	9	Availability of cost-efficient, profitable alternative treatments.
	<ul style="list-style-type: none"> Stimulate the development of alternatives for AB 		
	<u>Biosecurity</u>		Availability of cost-efficient, profitable alternative treatments; Investments in infrastructure; Quality of stockmanship; Access to antibiotic counselling.
	<ul style="list-style-type: none"> Stimulate and refine initiatives to improve biosecurity on farms Increase use of vaccines and stimulate biosecurity 		
Strengthen the One Health approach at all levels	<u>Welfare</u>	9	Animal health and welfare; Intensity of livestock production.
	<ul style="list-style-type: none"> Enhance the cooperation between veterinarians and technicians⁹⁹⁹⁹ to improve infrastructure/management on farms, plus prevention Upgrade the importance of animal welfare in the need to use AB Improve implementation specific welfare regulation, e.g. stocking density and weaning age 		
	<ul style="list-style-type: none"> Learn from each other's successes and failures 		Farmer's receptiveness to guidelines for prudent antibiotic use; Vet's receptiveness to antibiotic prescription guidelines.
	<ul style="list-style-type: none"> Specify a sensitization structure to improve receptiveness of operators (vets and farmers) Appreciate the full understanding of the One Health approach (interdependencies between human – animal – environment) 		

⁹⁹⁹⁹ The term technicians refers here to the advisors of all kinds of companies, e.g. feed mills, but also stable builders, ventilation experts etc.



Cluster	Suggestions	Nr of votes in the plenary	Related concepts in the systems map
	<ul style="list-style-type: none"> Integrate human and vet AB policy into 1 single transversal and independent body in which all stakeholders are represented 		Ability to organisationally embody a One Health approach.
Stimulate veterinary antibiotic stewardship	<ul style="list-style-type: none"> Impose and support coaching for farms with respectively high and moderate AB use Push back use of antibiotic without diagnosis by veterinarians through regulation Increase pressure on operators (vets and farmers) by individual benchmarking Enforce centralization of AST (antibiotic sensitivity testing) resulting in sector-specific and geographically detailed data on AMR Communicate prudently about antibiogram testing, i.e. not to facilitate use of critically important ABs 	7	Access to antibiotic counseling; Availability of benchmarking.
Further develop and continue the current initiatives		3	
Adapt market access of AB to context of AMR	<ul style="list-style-type: none"> Soften the regulation requirements for older molecules to fill in therapeutic gaps – based on established use Implement control of internet sales and harmonize in EU and globally 	2	Availability of old antibiotics.
Increase stringency of controls	<ul style="list-style-type: none"> Improve controls at farm level 	2	Stringency of controls
Stimulate level playing field	<ul style="list-style-type: none"> Lay down minimal (inter)national rules for hygiene and biosecurity 	0	International consensus on list of critically important antibiotics; International coherence of antibiotic guidelines.
Direct consumer pull towards AB free products	<ul style="list-style-type: none"> Develop markets for AB free (never-ever) product labels 	0	Pressure of retailers to reduce antibiotic use; Consumers' willingness to pay premium for antibiotic free food.

AB: antibiotics; AMR: antimicrobial resistance; AST: antibiotic sensitivity testing



Summary of the discussion

The subgroup had a very good discussion and showed a lot of openness. Several suggestions were clustered around improving disease prevention (by alternative pharmacotherapeutic treatments and improving bio-security and animal welfare). There was also a general consensus that in the veterinary sector there is a need for antibiotic stewardship with regard to veterinary antibiotics prescription and use. This includes coaching farmers on the ground. In general, there was a lot of openness in the veterinary team to learn from the human side. The semantics of antibiotic stewardship are well known in the animal sector. Strengthening the One Health approach was also mentioned, so that there is an exchange in both directions. There are close interdependencies between animal and human environments and the group would like to see a full understanding and operationalisation of the One Health approach.

There was also a specific cluster on consumer behaviour, more specifically directing the consumer pull towards antibiotic free animal products, particularly through labels. This also connects with increasing the stringency of controls at the farm level.

Another interesting cluster is related to economics: adapt market access of antibiotic to the context of antimicrobial resistance, for example by tailoring the registration requirements. At the end of the discussion, a plea was made to continue initiatives that are already ongoing and strive for a full deployment of those measures.

Prioritisation by voting: Three clusters of suggestions received markedly more votes compared to others. The prioritisation of on-farm stewardship and disease prevention and the suggestion to take animal welfare as a guiding principle is indicative of a desire to reinforce bottom-up interventions at the farm level oriented towards farmers, veterinarians and technicians who are doing the daily work. There is a strong call to reinforce the One Health approach to facilitate exchange of information, develop stronger messages and more effective national policy institutions.

Match with the systems map: the suggestions offered by the stakeholders centre on factors feeding into key concepts in four clusters. These are 'farmer's receptiveness to guidelines for prudent antibiotic use', 'Prudence

of veterinary antibiotic prescription'; 'Availability of cost-efficient, profitable alternative treatments' and 'Effectiveness of antibiotic policy'.

7.6 Discussion

General thrust of the suggestions for improvement

If the suggestions offered by stakeholders to improve antibiotic policy and prudent antibiotic prescription and use are considered all together, it turns out that his group of stakeholders is convinced that efforts need to be directed where 'the rubber hits the road', i.e. at the heart of the daily practice of medical professionals, vets and farmers. The efforts to move towards responsible and prudent use of antibiotics needs to mesh with the daily grind on the farm, on the hospital floor, and in practitioners' cabinets. Many tools and supports are already available. Guidelines may not be perfect, but they're there and they need to be made accessible and centralised to inform daily clinical decision making. Four interrelated key supports need to make sure that this happens: Informational, operational, financial, and human support. Provision of high quality (timely, reliable, relevant to the setting) guidelines and high quality data on prescribed volumes and types of antibiotics (and the corresponding diagnoses), are key requirements. They need to be the basis for up-to-date and smart decision support systems, easy to access for practitioners in any setting. For ambulatory care practitioners, the electronic prescription platform could hold great promise. It could allow practitioners easy and immediate access to all necessary information to support rational prescription (guidelines, regulations, local ABR patterns), and this tool would be an excellent vehicle to design appropriate (financial) incentives for practitioners to adopt more prudent use of antibiotics. In hospitals, data need to be the basis for evolving targets which are coupled to 'pay-for-quality' financing. Also the human dimension is a key element of this antibiotics-focused 'information system'. Infectiologists (who are not officially approved yet in Belgium) must be able to intervene in any ward, ambulatory practitioners must be able to learn and receive feedback from peers in a 'no blame' environment, vets need to be able to engage in long-term counseling relationships with farmers and technicians. It is in these finely granular human interactions that a culture of responsible use (properly speaking 'a culture of stewardship') of antibiotics takes shape. This seems to be the core idea that underpins stakeholders'



suggestions emerging from this consultation process. This is not a matter of pitting 'top down' against 'bottom up' measures. Strategic decisions at policy level will be needed to create the right environment for this culture to flourish: they need to be coherent and transparent, make sure the information is there, targets are set, incentives are designed and funding is available. The group deliberating suggestions for the ambulatory sector did, however, advocate important changes in basic aspects of the Belgian health care system.

A number of elements were weakly profiled in stakeholder suggestions. The patient or consumer as empowered, health-literate agent does not play an important role in these suggestions. The contribution of sensitisation campaigns was perhaps less foregrounded than what could be expected. Finally also the role of pharmaceutical companies, and the wider market dynamics they co-create, has not been considered as a leverage point. The veterinary subgroup in this workshop made a strong case for a more energetic operationalisation of the One Health approach, but this was not echoed by the stakeholder groups pondering suggestions for the human side. Nevertheless, as someone in the concluding plenary discussion pointed out: "Very few people from the human sector are aware that every AB-prescription handed out to a farmer is registered and centralized. Physicians are not aware of that. SANITEL-MED is a unique programme in that respect."

Strengths and weaknesses of this work

We assess the main strengths of the systems mapping effort as follows:

- The map provides an encompassing and finely granular overview of a complex system with a bearing on antibiotics prescription behaviour from a One Health point of view;
- The map was developed based on input from a range of stakeholders, including many key experts and decision makers in the Belgian antibiotics system;
- The systems map was productively used to support a process of stakeholder engagement in a politically sensitive context. The workshops organised to review the systems map and to generate suggestions for improvement of the Belgian antibiotics policy involved the active participation of stakeholders, allowed the group to comment

on individual suggestions (vs. only interviews) and to come to some level of consensus;

- The map-based stakeholder engagement process resulted in a prioritised set of suggestions for improvement, reflecting expert experiences from the field, which can be useful to policy makers;
- An assessment of the scope of the systems map revealed that there is a significant convergence between the concepts included in the map and determinants of prescription and use behaviour identified in the literature.

The work's main weaknesses are the following:

- The systems map reflects the statements made by a limited sample of stakeholders. It will therefore not be all-encompassing;
- Not all stakeholder groups were represented in the interview sample and in the group of participants involved in the workshops. A representative with a patient perspective was not included (but this choice was due to the acute form of common infectious diseases for which no patient organisation exists). Also, on the veterinary side, the pet sector was insufficiently represented. This results in a relatively marginal presence of pet-related concepts in the map (there are only two concepts that refer to pets: 'Antibiotic prescription for pets by ambulatory practitioners' and 'Strength of veterinarian independence in relation to pet owner');
- The systems map reflects the specificities of the Belgian context and will only be partially relevant for other settings;
- Related to the analysis of the veterinary sector, we acknowledge the fact that statements related to livestock (as opposite to companion animals) and pig farming (to the detriment of the other food-producing animals, such as poultry, laying hens, dairy cattle, veal calves, etc.) dominated in the interview material. One interviewer had expertise on fish farming. The map does not make explicit reference to the type of animal to which a given concept relates;



- The large number of concepts included in the map make for a complex diagram that may be difficult to navigate. (This report includes a narrative reading guide to complement the visual representation for people uncomfortable with the latter);
- The suggestions for improvement reflect expert opinion but have not been assessed for impact and feasibility.

7.7 Conclusion

The governance of the use of antibiotics is a politically sensitive topic in Belgium. In this process a diverse group of stakeholders – with representatives from intersectoral coordination bodies, public health administrations, hospital and ambulatory care practice, veterinarians and farmers, and pharmaceutical companies – was consulted to collect suggestions to improve antibiotic policy and strengthen prudent antibiotic prescription and use. Stakeholders were interviewed and their viewpoints were synthesised in a systems map. The map offers an integrated view of the factors that influence the prudent use of antibiotics for humans and animals. The systems map was reviewed by stakeholders and subsequently used to facilitate a brainstorm and prioritisation of suggestions/improvements deemed necessary to move towards more prudent use of antibiotics. The reflection was structured in terms of three subsectors: veterinary, hospital care for human and ambulatory care for human. The underlying thrust of stakeholders' suggestions for improvement is the wish to strengthen the One Health approach and a genuine culture of antibiotic stewardship across all sectors, based on informational, operational, financial, and human supports at the locus of clinical and therapeutic decision-making. This requires both 'top down' and 'bottom up' measures. Strategic decisions at policy level will be needed to create the right environment for this culture to flourish: they need to make sure the information is there, targets are set, incentives are designed and funding is available.

Key messages

- A systems map has been developed offering an integrated view of the factors influencing prudent prescription and use of antibiotics in humans and animals.
- Highlights from the stakeholder consultation are: guidelines need to be made easily accessible to inform daily clinical decision making; the electronic prescription platform could facilitate incentives for practitioners to adopt more prudent prescription of antibiotics; infectiologists must be recognised and should be able to give on-site advice in hospital wards; ambulatory practitioners must be able to learn and receive feedback from peers in a 'no blame' environment; vets need to be able to engage in long-term counseling relationships with farmers and technicians.
- From the systems map and the stakeholder consultation it is clear that the One Health approach is so far only a theoretical concept: a genuine culture of antibiotic stewardship across all sectors is desirable, but not yet put in practice.
- The core idea underpinning stakeholders' suggestions is that strategic decisions at policy level are needed to create the right environment for a culture of responsible prescription and use to flourish. Hence, a combination of top-down and bottom-up initiatives are needed to improve the current situation.



8 OTHER CHALLENGES WITH REGARD TO ANTIBIOTIC POLICY IN BELGIUM

8.1 Access to the right antibacterial product not straightforward

8.1.1 Background

As was elaborated above, the rise of AMR is accelerated by excessive antibiotic use in the human as well as in the veterinary sector. Yet, another vital component in the battle against AMR is access, more precisely access to the right antibacterial product. Access may be hindered by the fact that the (old) antibiotic is **not (longer) available on the market**. A recent survey^{hhhh} on the availability of 36 systemic antibiotics selected for their ability to treat infections caused by resistant bacteria and their unique value for specific criteria, revealed that the number of available antibiotics differed considerably from one country to another (i.e. from 7 antibiotics in Estonia to 24 in France).⁴⁴⁸ In Belgium only 14 of the 36 selected antibiotics were marketed. Economic motives were the major reported cause for absence of marketing of these antibiotics, including high registration costs and small market size (limited volume sales and low prices), leading to a perceived lack of return on investment for pharmaceutical companies (see also Box 29). Lack of demand (low use by clinicians as well as absence of recommendation of these drugs in national and/or international guidelines) and lack of awareness or low prioritisation of the problem by health authorities were also mentioned.

Box 29 – The broken antibiotic business model

Currently the **majority of antibiotics are generic**; only a small number remains on patent.⁴⁴⁹ Generally, new antibiotics, other antimicrobial medicines and vaccines are developed by either large research-based pharmaceutical companies or smaller biopharmaceutical companies. Yet, some large research-based pharmaceutical companies have generic medicine divisions (e.g. Novartis, Pfizer and Sanofi), and vice versa some generic medicine manufacturers also invest in R&D (such as Aurobindo, Cipla, Macleods and Mylan).⁴⁴⁹

The **antibiotics market** has a number of characteristics that makes it **financially unattractive to developers**. First, antibiotics are **less profitable** than other drug categories because of the current availability of multiple inexpensive generic antibiotics that have clinical utility for a majority of patients, incentives to use lower volumes of newer antibiotics to avoid overuse so that their clinical utility is maintained, reimbursement systems which encourage the use of the cheapest drug and the fact that antibiotics are often prescribed for a brief duration, while treatments for other indications (e.g. cancer or autoimmune diseases) can be more chronic and have higher profit margins.⁴⁵⁰⁻⁴⁵² Second, the **regulatory requirements** for market approval in the European Union and the United States have been **uncertain**, creating additional development risk.⁴⁵¹ Once new antibiotics reach the market, they will be tightly controlled to limit the risk of resistance emerging.⁴⁴⁹ Third, many pharmaceutical companies have **reallocated scientific talent and capacity** to more profitable opportunities, to the benefit of areas that may not be 'easier' but that definitely have a higher commercial return. In oncology, for instance, there were close to 800 new products in the development pipeline in 2014, of which around 80 percent were potentially 'first-in-class' (according to the Tufts Center for the Study of Drug Development)⁴⁵³ – compared to a total antibiotic pipeline today of fewer than 50 products.⁴⁵⁰

^{hhhh} The survey was conducted in 2015 on behalf of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Antibiotic Policies (ESGAP) and included the 28 EU member states, Albania,

the Republic of Macedonia, Montenegro, Serbia, Kosovo, Switzerland, Iceland, Norway, US, Canada and Australia.⁴⁴⁸



Antibiotics also attract a very small and shrinking share of venture capital funds. Of 38 billion USD venture capital invested into pharmaceutical R&D between 2003 and 2013, only 1.8 billion USD was invested into antimicrobials research, with total investments falling by more than a quarter over that period, despite the issue of drug-resistance becoming worse and, at least recently, becoming better known by the public.^{54, 451} Economists apply the term '**market failure**' to describe situations where supply and demand do not come together efficiently and effectively. More details can be found in 'The review on antimicrobial resistance' (2016), chaired by Jim O'Neill.⁵⁴

Besides the absence of marketing, there are also repeated and prolonged **shortages of supply**ⁱⁱⁱ which hamper the availability of essential medicines, among which also certain antibiotics.⁴⁵⁵ Actually, antibiotic shortages are worryingly common; they have been reported on a global and national scale.⁴⁵⁶ A survey^{jjj} among 607 European hospital pharmacists (including 94 from Belgium) indicated that antimicrobial agents were most frequently affected by shortages.⁴⁵⁷ An evaluation of US antibacterial shortages disclosed that 148 antibiotics were in short supply between 2001 and 2013, with 22% of drugs experiencing multiple shortage periods.⁴⁵⁸ Less is known about antibiotic shortages in Europe.⁴⁵⁹

Shortages of antibiotics have been attributed to fragile supply chains: as there are few competitors at different stages of the chain, the failure or exit of even one factory, manufacturer or middle-man can lead the entire supply chain to collapse.⁴⁵⁶ Fundamentally, the antibiotic market has a financially unstable model with tough market and regulatory conditions. Several pharmaceutical companies have left the anti-infectives market in recent years.⁴⁴⁸ This has particularly affected the antibiotics market, mainly due to low profit margins, but also to other factors, such as the opportunity cost of using a production line for more profitable products. Further, for many antibiotics, there are fewer and fewer companies producing the active pharmaceutical ingredients (API) needed. The current API market is

concentrated in a few manufacturing companies in India and China, which means that supply is less able to quickly adapt to meet surges in demand, but also that failures at one manufacturing plant can quickly lead to shortages that can last months or years.⁴⁵⁶ In 2017, the worldwide shortage of piperacillin–tazobactam, an important antibiotic and β -lactamase inhibitor combination in the treatment of hospitalized patients with severe and resistant infections, is reported to be the result of damage to a single factory in China.⁴⁶⁰ Some even warn: without a competitive market, there will not only be more frequent shortages and quality issues, but the last few companies left in the market will have greater power to dictate prices.⁴⁵⁶

Last but not least, the **availability of paediatric-friendly formulations of certain antibiotics is limited**. For the small spectrum antibiotic penicillin V, for instance, there is anno 2018 no paediatric formulation on the Belgian market.⁷⁹ Flucloxacillin magnesium octahydrate syrup, a narrow spectrum beta-lactam antibiotic of the penicillin class, was from 2013 to 2015 not available during 612 successive days (cf. Table 51) while fosfomycin powder for oral suspension is produced in doses inappropriate for paediatric patients (i.e. 3 g sachets).^{79, 459}

At present, there is little information available about the exact consequences of antibiotic shortages on patients' outcomes.⁴⁵⁶ Yet, the inadequate availability of certain antibiotics has a **serious impact on antibiotic prescribing**: prescribers may be forced to use less optimal, often broad-spectrum antibiotics instead. For example, for sore throat, amoxicillin is prescribed instead of penicillin V and for the treatment of cystitis fluoroquinolones are used instead of nitrofurantoin or fosfomycin. Such alternatives may also be less effective, may have more adverse effects, and may drive the selection of resistance.⁴⁵⁹ Hence, the lack of availability of certain antibiotics is a threat to antibiotic stewardship. No medicines' regulatory agency can mandate a manufacturer to produce a specific product.⁴⁶¹

ⁱⁱⁱ Over 20 different definitions for drug shortages have been identified in the literature.⁴⁵⁴ According to the Belgian law, "a drug is unavailable when enterprises which are responsible for the marketing of the drug are unable to deliver that drug for an uninterrupted period of four days to the community pharmacies, hospital pharmacies, or wholesalers in Belgium."⁷⁸

^{jjj} The survey was conducted in 2014 by the European Association of Hospital Pharmacists; responses were received from 36 European countries. The number of respondents ranged between 1 and 105 per country.



8.1.2 The availability of antibiotics in Belgium

In Belgium, the Federal Agency for Medicines and Health Products (FAGG – AFMPS) keeps track of medicines with (temporary) supply problems. The list of affected medicinal products is available online at <https://banquededonneesmedicaments.fagg-afmps.be/#/query/supply-problem/human> and is updated every working day. According to the Belgian law, holders of the authorization of the reimbursement of medicines must inform FAGG – AFMPS about the temporary unavailabilities that are expected to last more than 14 days at the latest within seven days after the start of the unavailability.⁷⁸ Local unavailabilities (e.g. due to a local distribution problem) are exempt from this obligation. An unavailability of more than one year is considered a temporary marketing cessation. The correctness of the (temporary) supply problem list is of course dependent on the readiness of pharmaceutical companies to share the relevant information and to do this in due time.

Within FAGG – AFMPS a **dedicated working group**, with representatives of RIZIV – INAMI, pharmacists, hospital pharmacists, pharmaceutical companies and distributors, has been composed to reflect on preventive measures as well as to find solutions for unavailabilities of medicines. One of the measures taken so far is the creation of a unique platform, a web-based application that will improve communication on unavailabilities. This application will cover two major parts, on the one hand the exchange of information between pharmacists and wholesaler (-distributors) and marketing authorization holders, where in case of an alleged unavailability of a medicinal product the pharmacist or wholesaler (-distributor) can contact the marketing authorization holder. In a later phase also prescribers will be able to report unavailabilities. The second part concerns the exchange of information between marketing authorization holders and FAGG – AFMPS. At present the reporting of unavailabilities is a time-consuming process for all parties involved (through forms available on the website which are then entered manually in a database). The platform will thus offer enormous

added value both for the license holders and for FAGG – AFMPS. The platform should be operational by the end of 2018. Another initiative taken by the dedicated working group is the development of a decision tree to estimate the seriousness of an unavailability and to find together with a dedicated taskforce adequate solutions (e.g. remaining stock, availability of medicines with the same active ingredient, availability of therapeutic equivalents, temporary importation from abroad) so that the impact for patients can be kept minimal. Last but not least, the FAGG – AFMPS working group is also looking for solutions to limit the quota restriction of medicines in Belgium and to facilitate the availability of alternatives from abroad in case no solution can be found at the national level. (FAGG – AFMPS, *personal communication*)

It was considered beyond the scope of the current project to perform an exhaustive analysis of all antibiotic supply problems listed on the FAGG – AFMPS website. Yet, the database was consulted in a pragmatic way: (temporary) supply problems mentioned during the interviews with stakeholders (i.e. Peni-Oral[®], Staphycid[®], Penadur L.A.[®], Azactam IV[®], Avelox IV[®], Negaban IV[®], Obracin IV[®], Pentrexyl[®], Biclar IV[®], and piperacilinetazobactam fresenius IV[®]) were explored in order to illustrate the Belgian situation of what is described in section 8.1.1. In addition, the availability of narrow spectrum antibiotics^{kkkk} was also explored, as their unavailability may result in the choice of a broad spectrum alternative (Table 51).

^{kkkk} The definition of narrow spectrum antibiotics is based on the 2017 ECDC, EFSA and EMA Joint Scientific Opinion on a list of outcome indicators as regards surveillance of antimicrobial resistance and antimicrobial

consumption in humans and food-producing animals⁴⁶²; according to that report it includes penicillin (ATC code J01CA, J01CE and J01CF), first generation cephalosporin (J01DB) and the macrolide erythromycin (J01FA01).



Indeed, several long-term antibiotic supply problems occurred from 2013 to 2018 in Belgium. At least one of the amoxicillin products, a narrow spectrum antibiotic, was unavailable every year and amoxicilline Mylan® (16 or 24 units) was even unavailable for nearly 4.2 years. Other narrow spectrum antibiotics, as flucloxacillin (612 days), benzylpenicillin benzathine (527 days) or penicillin V (133 days) were also commonly unavailable between 2013 and 2018 in Belgium (Table 51).

Table 51 – Examples of temporary supply problems and marketing cessations of antibiotics in Belgium (2013 – 2018)

Antibiotic	2013 ^s	2014	Number of days with supply problem			
			2015	2016	2017	2018*
Ampicillin (Pentrexyl®), 2g – 250 mg, solution for injection/infusion	0	0	0	0	0	/ [#]
Amoxicillin Trihydrate (Amoxicilline Mylan®), 500 mg, capsule, 16 units	180	364	364	365	246	0
Amoxicillin Trihydrate (Amoxicilline Mylan®), 500 mg, capsule, 24 units	180	364	364	365	246	0
Amoxicillin Trihydrate (Amoxicilline Sandoz®), 500 mg, capsule, 16 units	0	0	0	0	32	18
Amoxicillin Trihydrate (Amoxypen®), 1g, effervescent tablet, 8 units	0	0	364	32	0	0
Amoxicillin Trihydrate (Amoxypen®), 1g, effervescent tablet, 20 units	0	0	364	32	0	0
Amoxicillin Trihydrate (Flemoxin®), 250mg/5ml	0	16	47	0	0	0
Benzylpenicillin Benzathine (Penadur L.A.®), 1.200.000 IU, powder and solvent for solution for injection	0	0	95	23	45	364°
Cefadroxil (Duracef®), 250mg/5ml, powder for oral suspension	0	0	0	121	212	0
Cefadroxil (Duracef®), 500mg, capsule, 16 units	0	0	0	152	212	0
Cefadroxil (Duracef®), 500mg, capsule, 100 units	0	0	143	0	0	0
Cefadroxil Monohydrate (Cefadroxil Sandoz®), 250mg/5ml, powder for oral suspension	0	0	0	275	205	0



Antibiotic	2013 ^s	2014	Number of days with supply problem			
			2015	2016	2017	2018*
Cefadroxil Monohydrate (Cefadroxil Sandoz®), 500mg/5ml, powder for oral suspension	0	0	0	275	205	0
Cefazolin Sodium (Kefzol 1g® + Lidocaine), 3 x 1 g + 3 x 1 ml, powder and solvent for solution for injection	0	0	0	0	0	102
Clarithromycine Lactobionate (Biclar®), 500mg, powder for solution for infusion	0	0	19	35	22	0
Erythromycin Ethylsuccinate (Erythrocin®), 250mg/5ml, granules for oral solution	0	0	152	69	0	0
Flucloxacillin (Floxapen®), 250mg, powder for solution for injection	0	0	0	66	0	0
Flucloxacillin (Floxapen®), 500mg, powder for solution for injection	0	0	0	66	0	0
Flucloxacillin (Floxapen®), 1g, powder and solvent for solution for injection, 3 x 1 g + 3 x 4 ml	0	0	81	66	0	0
Flucloxacillin (Floxapen®), 1g, powder and solvent for solution for injection, 10 x 4 ml	0	0	115	0	0	0
Flucloxacillin magnesium octahydrate (Staphycid®), 250mg/5ml, syrup	112	364	136	0	0	0
Oxacillin Sodium (Penstapho infection®), 1g, powder for solution for infection	0	0	73	0	0	0
Phenoxymethylpenicillin potassium (Peni-Oral®), 1.000.000 IU, tablet	0	0	0	0	133	0
Piperacillin Sodium/Tazobactam Sodium, produced by Fresenius Kabi, 4g – 500mg, powder for solution for infusion	0	0	0	0	10	0
Moxifloxacin Hydrochloride (Avelox®), 400 mg, film-coated tablet, 5 units	0	0	0	0	24	54
Moxifloxacin Hydrochloride (Avelox®), 400 mg, film-coated tablet, 10 units	24	0	0	0	72	154
Moxifloxacin Hydrochloride (Avelox®), 400 mg, film-coated tablet, 80 units	0	0	64	0	0	67



Antibiotic	2013 ^s	2014	Number of days with supply problem		2017	2018*
			2015	2016		
Moxifloxacin Hydrochloride (Avelox®), 400 mg/250 ml, solution for infusion	0	0	0	128	68	39
Temocillin Sodium (Negaban®), 1g, solution for injection	0	0	0	0	40	0
Temocillin Sodium (Negaban®), 2g, solution for injection	0	0	0	0	30	0

^s: 2013 data may be incomplete since unavailabilities have been entered in the database in a structured way from 2014 onwards; *: 2018 data may be incomplete as the list was consulted on 3 May 2018; ^oPredicted to be unavailable until the end of 2018; [#]No longer marketed since October 2017.

Source: <https://banquededonneesmedicaments.fagg-afmps.be/#/query/supply-problem/human>

Key messages

- Access to the right antibacterial product may be hindered by the fact that the (old) antibiotic is not (longer) available on the market, that it is temporarily unavailable or that a formulation of an antibiotic suitable for children is not available in the correct dosage;
- Several long-term antibiotic supply problems occurred from 2013 to 2018 in Belgium, affecting the availability of (among others) narrow spectrum antibiotics.

8.2 Mismatch between antibiotic package size and guidelines for their use leading to self-medication

One of the other pitfalls that was raised during the interviews with stakeholders and during the workshops (see chapter 7) is the problem of the mismatch between antibiotic packaging and the guidelines for their use. The most cited example being nitrofurantoin in the treatment of acute uncomplicated cystitis for which a total of 9 tablets of 100 mg are needed in adults, while the available package either contains 50 tablets of 50 mg or 50 tablets of 100 mg (see Table 52).¹⁵⁴ But also in case of abscesses of odontogenic origin with systemic symptoms, the prescriber is not able to match his prescription with what is recommended in the BAPCOC guideline.¹⁵⁴ This mismatch burdens the patient after his treatment with a left-over of antibiotics. This is a problem that has also been raised in other countries. In Australia, for instance, the match between package size and the posology described in the guideline was only confirmed for 4 out of the 32 most commonly prescribed antibiotic-prescribing scenarios in ambulatory practice.⁴⁶³



Table 52 – Examples of mismatches between antibiotic packaging and guidelines for their use

Antibiotic	Infection indication	Amount needed according to BAPCOC guideline ¹⁵⁴ and/or BCFI – CBIP 2018 ⁷⁹	Amount included in the package (with the best match) according to BCFI – CBIP 2018 ⁷⁹	Left-over (+) or shortage (-)
Nitrofurantoin				
	Acute uncomplicated cystitis	9 tablets of 100 mg	50 x 50 mg	32 x 50 mg (+)
			50 x 100 mg	41 x 100 mg (+)
Metronidazol [§]				
	Trichomonas vaginalis	2 g (taken in 1 dose) or	20 x 500 mg	16 x 500 mg (+)
		1 g/day during 7 days	20 x 500 mg	6 x 500 mg (+)
Amoxicillin				
	Abscess of dental origin*	1-2 g/day during 3-5 days (i.e. 6 x 500 mg (or 3 x 1 g) up to 20 x 500 mg (or 10 x 1 g))	8 x 1 g	5 x 1 g (+; in case of the minimal posology)
			16 x 500 mg	4 x 500 mg (-; in case of the maximal posology)
			30 x 500 mg	10 x 500 mg (+; in case of the maximal posology)

*§: Metronidazol is stricto sensu an antiprotozoal (ATC code P01AB), yet it is also active against anaerobic bacteria; * An abscess of dental origin needs dental treatment, but in case it is associated with fever and/or evidence of systemic spread (e.g. proliferation of lymph nodes, trismus or facial cellulitis), empirical antibiotic treatment is indicated as adjunctive therapy.⁴⁶⁴*

Studies indicated that the availability of leftover antibiotics is a major source of self-medication.²³³ These leftover antibiotics may result from the dispensation of a larger number of tablets than needed for one single course, but also from non-compliance of patients (see also section 5.1.3.2). Whatever the cause, self-medication with antibiotics is inappropriate because of the possibility of an incorrect choice of antibiotics, of insufficient dosages or of unnecessary therapy.²³⁸ Using leftovers for a later infection in the same patient carries a double risk: the subsequent pathogen may not share the susceptibility of the previous one and the medication may have lost potency due to improper or prolonged storage, thus creating an

environment of subtherapeutic dosing.²³⁰ But even when leftover antibiotics are discarded, they add to the problem of environmental pollution. Therefore, unlike most other drugs that in case of incorrect use may simply pose a risk to the particular patient, the inappropriate use of antibiotics adds to the global risk of increased spread of resistance.²³⁰



A global survey^{III} of outpatients who had taken self-administered antibiotics pointed out that regardless of the geographic region, the strongest predictor for saving leftover antibiotics or giving them away was the antibiotic dispensing system of the country.²³⁰ In countries where antibiotics were dispensed per package size, respondents had a four times higher risk of having leftover antibiotics and a five time higher risk of saving them and giving them to someone else.²³⁰ A European survey^{mmmm} confirmed that at the country level, the exact dispensation of prescribed tablet quantities by pharmacies was independently associated with a lower likelihood of self-medication (OR 0.51, 95% CI 0.27-0.98).²³⁴

An effective way of preventing self-medication with antibiotics is the **prevention of leftovers** from prescribed courses. This can be implemented by the **dispensation of exact numbers of antibiotic tablets in pharmacies through fractionation**, as is already the case in the UK, the Netherlands (Box 9), US, Japan, Israel and the Czech Republic.^{217, 230, 238}

Box 30 – The dispensation of exact numbers of antibiotic tablets in pharmacies – the example of the Netherlands

Since more than two decades, the exact number of antibiotic tablets are dispensed in pharmacies in the Netherlands. When indicated, packages are broken up: the tablets are dispensed in a blank box and the pharmacist has to store the leftover tablets in the original (broken up) package. The information leaflet for the patient is printed or copied.

Source: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP), Geneesmiddel Informatie Centrum (personal communication)

At present **fractionation of medicines is current practice in Belgian hospitals** where the hospital pharmacies deliver medicines per unit to the patients. But also in **pharmacies open to the public**, pharmacists are **since 2006 authorized to fractionate medicine packages**, provided that certain conditions are met:¹²⁶

- there is no adequate primary package size of the medicinal product, licensed and marketed in Belgium, for the duration of the treatment for which it is prescribed;
- only larger packages can be transferred to smaller packages;
- no change is made to the properties of the medicine;
- the pharmaceutical form of the medicine is not changed;
- the expiry date stated on the original package is respected.

Currently, the fractionation in pharmacies open to the public is in practice within the framework of detoxification programmes, where the whole content of the package is delivered to the same patient and paid by the patient at the first delivery. The pharmacist issues the number of prescribed drugs and will issue the following, which he keeps, at a next prescription.

Upon inquiry with FAGG – AFMPS it appeared that there are still barriers to be taken in order to extend the fractionation of medicines to e.g. antibiotics: prices and reimbursement rules have to be adopted (these are set now per package and not per unit), computer systems used by pharmacists have to be adapted (which currently only record the delivery of a box of medicines to one patient and not to several) and prescribers have to be informed. With regard to the financial aspects, the billing rule for nursing home residents issued in 2015 can be a source of inspiration (see section 6.1.1.4). If fractionation of medicines is indeed extended to e.g. antibiotics and in all

^{III} Data were collected using a standardised, structured, interviewer-administered questionnaire in 11 countries: Brazil, China, Italy, Japan, Mexico, The Netherlands, The Philippines, Russia, South Africa, Turkey and the USA.²³⁰

^{mmmm} Data were collected between October 2003 and May 2004 using face-to-face structured interviews in 12 countries, which were selected to represent

Northern/Western (Austria, The Netherlands, Sweden, the UK and Belgium), Southern (Italy, Malta, Israel and Spain) and Eastern (the Czech Republic, Lithuania and Croatia) European regions. Because of data collection problems, Spain was excluded from the analyses.



settings, FAGG – AFMPS will also have to adapt its supervision (e.g. the expiry date, the patient leaflet). (FAGG – AFMPS, *personal communication*)

Last but not least, another aspect which is related to the mismatch between antibiotic package size and the guidelines for their use, is the fact that over the last years, the number of DDDs (defined daily doses) per package substantially increased for the most commonly used antibiotics in Belgium, but also in other European countries.^{93, 102} This increase in package dosage distributed by the pharmaceutical industry happened while guidelines did not necessarily recommend higher doses or longer treatment durations.

Note:

It was suggested by some stakeholders to solve the problem of the mismatch between the antibiotic pack size and the guidelines for their use by simply adjusting the package size of antibiotics to the instructions in the guidelines. However, upon inquiry with FAGG – AFMPS it appeared that pharmaceutical firms cannot be forced to apply for the authorisation of alternative package sizes, and even if they have the authorisation, making this package size available on the market cannot be enforced; hence this approach may not be effective. (FAGG – AFMPS, *personal communication*)

Key messages

- **The mismatch between the antibiotic package size and the guidelines for their use, leads to leftovers and potential self-medication;**
- **Since 2006, pharmacists working in pharmacies open to the public are authorized to fractionate medicine packages.**

8.3 Ethical challenge: individual vs. collective responsibility

Although this report does not cover the ethical aspects of the prudent use of antibiotics, an important element that influences whether an antibiotic will be prescribed by the practitioner in human medicine and/or used by the patient relates to the approach under which this decision-making process is made: the needs of the individual or the collective perspective.⁴⁶⁵ The strongest motive to restrict antibiotic use, and especially the use of broad-spectrum antibiotics, is to slow the rapid rise in resistance.⁴⁶⁶ On one hand, the physician and the patient want the disease to be cured. On the other hand, the emergence of antibiotic resistance will pose a risk to the collectivity, and we may face a time where people will die from infections because of a lack of effective drugs. If only the patient is considered and the cost of resistance is ignored, a maximum antibiotic treatment would probably be prescribed for each patient.⁴⁶⁶ And if nothing is done to fight against antimicrobial resistance, future patients will be deprived of potentially lifesaving drugs.⁴⁶⁵ Any drug prescription should take into account the balance between the therapeutic benefit and the adverse effect of the drug for the patient. But in the case of antibiotics, the decision should take into account the balance between the *immediate* benefit and safety for the individual patient and the *future* lack of therapies for the community. These decisions encompass governmental and professional institutions, as well as prescribers and their patients.⁴⁶⁵

A specific aspect of this decision relates to the empirical treatment of patients, i.e. the treatment without knowledge of the pathogen or its susceptibility. Most guidelines adopt an empirical approach. These guidelines do not intend to cover the entirety of the possible pathogens causing diseases.⁴⁶⁶ The proportion of patients with acute infection in whom the etiologic cause(s) of the infection is covered by the empirical therapy should ideally be 100%, as it is known that inappropriate empirical therapy is a risk factor for mortality.⁴⁶⁷ The ethical question here becomes whether current patients at risk might be given less than maximum treatment in order to benefit future, unidentified patients.⁴⁶⁶ Or should empirical treatment be overly broad for the majority of patients just to save a few? This dilemma is particularly encountered by prescribers in settings such as intensive care units, where patients are at higher risk of dying from infections. Some authors argue that future patients have a right to come to a minimal harm.⁴⁶⁶

**Key messages**

- Tackling antibiotic resistance through prudent antibiotic use requires a collective approach, in which the immediate benefits for the patient (optimal treatment of infections) should be weighted against the future harms of the community (resistant strains).

9 JOINT EC – ECDC ONE HEALTH COUNTRY VISIT TO BELGIUM – KEY ISSUES WITH REGARD TO ANTIBIOTIC USE

The European Centre for Disease Prevention and Control (ECDC) and the European Commission's Directorate-General (DG) for Health and Food Safety jointly carried out a country visit to Belgium from 16-24 November 2017 to discuss antimicrobial resistance (AMR) issues. The visit was performed at the request of the Belgian authorities to assist them in the further development and implementation of their national policies and strategies for tackling AMR based on a One Health perspective. The visit was carried out by two teams, with some joint meetings and visits where possible, with the ECDC team focussing on human health issues while the DG Health and Food Safety team covered veterinary (and environmental) aspects. The findings of the country visit were summarized in two separate reports produced by ECDC and DG Health and Food Safety covering each of the areas respectively.^{76, 80}

In the following sections, we summarised the most important findings of both reports. While the country visit addressed antimicrobial resistance, we limited our summary to the prudent use of antibiotics in Belgium, as this is the scope of the present KCE report.

9.1 Human health – ECDC

9.1.1 Observations made by ECDC

To assist member states in implementing the Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC) which outlines the threat that AMR poses to human health and advocates for a range of actions to be taken for its prevention and control, ECDC has developed a process for country visits aiming to assess and discuss the national situation regarding prevention and control of antimicrobial resistance (AMR) through prudent use of antibiotic and



infection control.⁵² To that end, an assessment tool, with ten topics, has been developed; it guides the discussions during the visit.

9.1.1.1 *Development of an intersectoral coordinating mechanism*

Although BAPCOC was one of the first examples of an Intersectoral Coordinating Mechanism in Europe, the Royal Decree that sets out its legislative framework did not explicitly address the allocation of financial resources to different institutions or projects, meeting frequency or targets (including its own monitoring and evaluation).⁷⁵

BAPCOC issued a policy paper for the 2014-2019 term (see Box 10), outlining policies to improve antibiotic consumption and appropriateness of antibiotic prescriptions. However, ECDC highlighted several gaps in the strategy and specified that actions are somewhat generic and often lack milestones, deliverables and timelines and that executive players and resources are not clearly identified and earmarked.

According to the ECDC team, it is also unclear how BAPCOC's advice is being translated into regulatory action at the national and regional levels, what the remit of the FOD – FPS Public Health's responsibilities linked to BAPCOC's recommendations is and how BAPCOC and Sciensano (formerly WIV – ISP) interact and define their roles in surveillance and scientific advice on AMR. ECDC also noticed that the presence and role of the veterinary sector within BAPCOC is limited.

The constitution of a task force to develop a national strategic plan 'to fight multidrug-resistant organisms' through an agreement protocol between the federal state and the federated entities is called 'a laudable ad-hoc initiative' in the ECDC report.

9.1.1.2 *Organised multi-disciplinary and multi-sectoral collaboration at local level*

Although hospitals are required by Royal Decree (26/04/2007) to have a Hospital Hygiene Committee and a Hospital Hygiene Team,⁴⁶⁸ and to set up a multidisciplinary antibiotic management team (GGA/ABTBG),²⁷⁸ not all healthcare facilities visited by the ECDC team, placed AMR control as a priority. The ECDC team encourages to increase the commitment of hospital managers to understand and provide the resources needed to combat AMR and promote prudent use of antibiotics.

The ECDC reporters further signalled that doctors with the appropriate competence in the area of infectious diseases or clinical microbiology, who give advice on antimicrobials feel that their role is not acknowledged, as their verbal and written advice to other doctors is not recorded as a consultation and does not count for the purposes of reimbursement. This observation is probably related to the fact that (unlike the vast majority of EU countries) medical specialisations in infectious diseases and medical microbiology are not legally recognised in Belgium.

In nursing homes (NHs), each resident has the choice of his own GP, which may result in an inconsistent approach to the diagnosis and management of infections, with an overuse of antibiotic and a tendency to overuse broad-spectrum antibiotics in particular. The 'coordinating and advising physician' ('coördinerend raadgevend arts' (CRA) – 'médecin coordinateur et conseiller' (MCC)) does not have any real possibility to train other GPs or to harmonise their diagnostic and prescription practices. ECDC highlighted that the implementation, monitoring and evaluation of evidence-based guidelines for the treatment of urinary tract infections would already represent a significant step forward in terms of antibiotic stewardship in NHs.



9.1.1.3 *Monitoring of antibiotic usage*

Even though antibiotic use in the ambulatory sector is monitored, the ECDC reporters pointed out that GPs and other physicians receive feedback on their own prescriptions with a two-year delay or sometimes more; that gap is not conducive to timely corrective action. They also noticed that Penicillin V (oral) is rarely prescribed in Belgium.

They welcomed the fact that in hospitals surveillance of antibiotic consumption moved from a passive system (i.e. the Antibiotic Use in Hospitals (ABUH) project), where pharmacists had to enter data on a website, to a new system (i.e. BeH-SAC, which stands for 'Belgian Hospitals - Surveillance of Antimicrobial Consumption') managed by Sciensano. In this system, data already reported to RIZIV – INAMI for reimbursement purposes will be fed back to hospitals and will be available for analysis of antibiotic prescriptions.

ECDC encourages to further develop utilisation of quality indicators on hospital antibiotic use by developing a monitoring and evaluation method through the automated e-prescribing software tool, for example, to assess compliance of prescriptions with local and national guidelines by linking prescription data (that must include an indication for the prescription) with electronic patient records.

9.1.1.4 *Antibiotic utilisation and treatment guidance*

GPs and hospital prescribers reported to the ECDC team that many GPs and other clinicians lack knowledge on the mode of action of different antibiotic, their indication and use. For instance, ECDC collected anecdotal evidence that doctors overprescribe quinolones for acute, uncomplicated urinary tract infections; amoxicillin-clavulanic acid for simple skin infections; amoxicillin rather than penicillin V for tonsillitis, or combinations of oral and topical antibiotics simultaneously. They did not collect information in dental practices.

ECDC further noticed that less emphasis has been placed on other methods aimed at changing behaviour such as those focusing on motivation/social norms.

All hospitals visited by the ECDC team reported that they had a rigorous process for producing evidence based antibiotic guidelines. However a study performed by BAPCOC in 2016, revealed that 20 % of the participating hospitals did not have a policy restricting selected antibiotic such as carbapenems.⁴⁶⁹ Compliance with guidelines varied among hospitals, with a mean of 80%, thus not reaching the target of 90% as defined in the BAPCOC policy paper.⁷⁷

ECDC identified several structural and procedural reasons that could explain the lack of implementation of the national evidence-based guidelines. Hospitals (especially small ones) lack doctors specialised in infectious diseases who can provide tailored advice on treatment. Interdisciplinary activities, such as providing advice in several different wards, are currently not acknowledged and clinicians often do not have the knowledge or the motivation to monitor and assess their antibiotic prescriptions. In NHS, the coordinating physician does not even have access to other clinicians' patient files and prescription records because of privacy rules. Other structural limitations include the limited availability of narrow-spectrum antibiotics, such as penicillin V, and lack of reimbursement of point-of-care testing such as C-reactive protein (CRP) rapid tests. In primary care, many GPs work independently, in single GP practices.

9.1.1.5 *Education programmes*

ECDC highlighted the absence of a specific course on AMR for undergraduate medical students. In addition, no compulsory education on antimicrobial stewardship is in place for GPs and other prescribers. ECDC also noticed no indication that GPs were using tools provided by BAPCOC. However they encourage BAPCOC's initiative started in October 2017 to provide e-learning modules on antimicrobial stewardship for GPs within the framework of compulsory continuous professional development (CPD) for medical doctors.



9.1.1.6 Public information related to AMR

ECDC cites Eurobarometer results showing that knowledge of AMR issues in Belgium rates around or higher than the European average a finding that ECDC links to the national public awareness campaigns on the prudent use of antibiotics. But ECDC observed that media coverage is imbalanced between the French, Flemish and German languages and that funds (€400 000/year) are limited. The ECDC team also gathered anecdotal reports that despite the public awareness campaigns targeting the general population, a significant number of patients still expect to be prescribed antibiotics even when this is not appropriate for their condition.

9.1.1.7 Marketing related issues

ECDC considered the influence of pharmaceutical companies on prescribing behaviour as significant, given for instance the prescription rates of moxifloxacin which is higher in Belgium than in other countries; a finding that can be explained by the influence of pharmaceutical companies on prescribers' practices in the past. In addition, ECDC noticed that prescribers experienced difficulties regarding the availability of some narrow-spectrum antibiotics, such as penicillin V.

9.1.2 Key recommendations made by ECDCⁿⁿⁿⁿ

Update the national intersectoral coordinating commission (BAPCOC)

A priority for BAPCOC would be to review and update its composition, mandate, tasks and lines of reporting. The respective remits of BAPCOC and Sciensano (formerly the Scientific Institute of Public Health) need to be complementary and should not overlap. In fact, it has been demonstrated that a holistic approach is essential to effectively curb AMR. A national Intersectoral Coordinating Mechanism should be multi-disciplinary, it should include a strong infection prevention and control component and a tangible presence of the relevant ministries. Therefore, BAPCOC should not limit its activities to antibiotic policy alone.

In addition, the **organisational aspects** should be updated in order to face the administrative difficulties and procurement issues which in the past have resulted in inefficiencies and difficulties in executing budget.

Adequate **resources** should be made available, such as ministerial staff and support from relevant ministries for handling the administration, procurement, coordination and secretarial tasks of BAPCOC.

Finally, composition of BAPCOC should **include complementary key actors**, such as representatives of long-term care facilities (LTCFs), nurses, patients and consumer groups.

Develop a national action plan based on the BAPCOC policy paper

The current policy paper from BAPCOC⁷⁷ should be transformed into a **comprehensive national action plan** following the **One Health approach**, in line with the Council Conclusions of 17 June 2016,⁴⁷⁰ and incorporating specific activities, a core compulsory set of AMR and Healthcare-associated infection (HAI) indicators, targets (including Infection Prevention and Control (IPC) targets that are now absent from the document), times and responsible entities (to increase the executive role of the relevant ministries).

The national action plan should cover human medicine (ambulatory/general practice, hospital and nursing homes sectors) and animal medicine, including vaccination policy. This action plan, once approved, will need to be supported and provided with the necessary resources for its implementation, preferably earmarked for each activity.

Promote compliance with evidence-based prescription guidelines

The electronic prescribing system represents an important opportunity for **faster feedback of prescribing practices to prescribers**, benchmarking and self-improvement of these prescribing practices through, for example, visits from peers to the highest prescribers of antibiotics. Similar experiences from other EU/EEA countries showed how successful peer-reviews are. However, information on the indication (type of infection) for each antibiotic

ⁿⁿⁿⁿ Limited to the scope of this KCE report, i.e. antibiotic prescription and use.



prescription would need to be reported in order for the monitoring and evaluation of e-prescriptions to be really effective.

In addition, the development of the e-health system represents an opportunity to **include decision support tools** in accordance with national guidance or warning in the event of inappropriate prescription.

To **preserve last-line antibiotics**, ECDC recommends that a national, harmonised policy be implemented for a restricted list of some antibiotics and that this should be mandatory. For example, prescription of certain broad-spectrum antibiotics could be restricted to specialists.

Introducing **targets**, increasing **access to narrow-spectrum antibiotics** (e.g. authorities ensuring that pharmaceutical companies market penicillin V) and making **antibiotic stewardship a mandatory discussion theme** in GP circles are potential and achievable interventions to effectively curb antibiotic use. Moreover, the results of clinical audits, which are rarely reported back to clinicians, could become part of a quality label for GPs, LTCFs and hospitals.

Although it is important to **assess compliance with guidelines**, this could include tailored advice and the guidelines themselves could be made more readily available. For example, they could provide evidence that broad-spectrum antibiotics are not more effective than narrow-spectrum antibiotics. Other possible effective interventions would be to create a network of pharmacists with training in antibiotic use, as well as promoting delayed/back up antibiotic prescription (especially useful when confronted with demanding patients), in parallel with safety netting. Finally, limited and conditional reimbursement, as has been proposed, among others, by FPS Health, BAPCOC and NIHDI for quinolones, would help limit usage and promote antibiotic stewardship and adherence to guidelines. *[Note: as is described in section 1.1.1.1, this has been introduced as of 1 May 2018 (i.e. after the ECDC visit)]*

Mandatory **audits** of antibiotic use, dose, duration and reason for prescribing as **part of the accreditation process** would help GPs and specialists understand and change their prescribing practices. In hospitals, coupling the audits with input and help by medical microbiologists and infectious disease specialists would increase prescribing appropriateness. Targets on antibiotic use could also be included in the 'pay-for-performance' system and would

contribute to promoting behaviour change via financial incentives. However, in order for these interventions to be effective, the government will have to encourage pharmaceutical companies to market narrow-spectrum antibiotics and address the current lack of supply of penicillin V (oral) and amoxicillin for intravenous injections.

As a minimum, specific challenges concerning **over-prescription for certain conditions**, such as inappropriate prophylaxis, antibiotic treatment of asymptomatic urinary tract infection (UTI) or overuse of fluoroquinolones, should be the focus of tailored antibiotic stewardship interventions. ECDC recommends that the results of these audits continue to be fed back through written reports with interpretation and advice in hospital and ambulatory sectors. GP-dedicated peer review groups or GP circles would be encouraged to discuss the results and challenges and to look at how antibiotic use could be improved.

The management of patients' expectations requires time for coaching and convincing patients and parents of young children that antibiotics may not be necessary. This time is not always available or a priority for GPs. Dedicated topics on antibiotic stewardship and patient communication as part of GP circle discussions could help GPs to tackle this issue.

Reinforcement of infectious disease clinicians' status and activity

Clinicians with appropriate knowledge and training about antibiotics and AMR, such as infectious disease specialists or medical microbiologists, are essential to ensuring appropriate treatment of infections, appropriate use of antibiotics and support for antibiotic stewardship programmes. **Infectious disease specialisation and consulting should be formally acknowledged** and consultations should be eligible for financial compensation.



Medical microbiology

Increased daily input by clinical microbiologists would improve the management of infections. This could be supported by automated comments, **automated pop-up antibiotic guidance** when receiving microbiology reports, and restrictive reporting of antibiotic susceptibility tests to encourage clinicians to use the correct antibiotic.

Awareness campaigns

According to ECDC national public awareness campaigns on the prudent use of antibiotics should be continued and should target both the general public and healthcare professionals. The campaigns should engage national and regional media with well-crafted stories, multiplying the messages around prudent use of antibiotics and the issues posed by AMR. Finally, traditional and social media should be monitored (the use of tools such as the European Commission (EC) Joint Research Centre NewsDesk could facilitate this task). Evaluation of the cost-effectiveness of the successive campaigns would help gather evidence for further action.

Compulsory education on AMR and antibiotic stewardship

Education on issues posed by AMR and the prudent use of antibiotics in the undergraduate and postgraduate curriculum should be compulsory. AMR topics, antibiotic stewardship and IPC should also be part of the continuous professional training for medical doctors and nurses, with a minimum biannual required attendance.

Strengthen the role of the coordinating physician in nursing homes

Each NH should have and implement clear antibiotic guidance, preferably placing emphasis on specific issues such as the treatment of urinary tract infections, asymptomatic bacteriuria and respiratory infections. Clear, short tables targeting the management of residents with dementia who have suspected infections or are carriers of Multidrug-resistant organisms (MDRO) would help to increase appropriate use of antibiotics.

9.2 Animal health - DG Health and Food Safety

9.2.1 Observations made by DG Health and Food Safety

9.2.1.1 Multi-sectoral collaboration and coordination, including one health approach

Although veterinarians are represented in BAPCOC's dedicated veterinary medicine working group, the visit team considered that in a One Health perspective it could be useful to have veterinarians included in some of the other working groups too, for example on awareness campaigns and infection prevention and control; this suggestion is based on experiences and good practices from other Member States.

Another problem the team noticed is the fact that the Royal Decree of 26 April 1999 describing the objectives, members and governance of BAPCOC,⁷⁵ does not describe any funding or source of funding. Currently, BAPCOC's budget is primarily sourced from public health funds and so practical difficulties are experienced in allocating these funds to veterinary or One Health activities.

The team highlighted the fact that few actions on the veterinary side were completed by BAPCOC from 1999 to 2011 and that integration of AMR surveillance and antibiotic (AB) use data from the human and veterinary domains remains outstanding and uncompleted.

9.2.1.2 Current status of Belgium's national action plan on AMR

In BAPCOC's 2014-2019 policy paper, the veterinary-related indicators and targets originate from AMCRA's 2020 strategic plan (see Box 10). The president of AMCRA has been a permanent member of BAPCOC's Bureau and BAPCOC is a member of AMCRA's Steering Committee.

The visit team further observed that since the Royal Decree of 21 July 2016 concerning critically important antimicrobials (CIAs, see Box 21)⁵⁷ and the tax on sales of veterinary antibiotics (see section 6.2.2.1, the working group has been in a dormant state but is now being reactivated in the light of possible actions that will be needed in the period beyond 2020 when



AMCRA's current strategy and vision document (and the Covenant on the use of antibiotics,⁸⁶ see section 6.2.2.1) concludes.

With regard to AMCRA's 2020 strategic plan, the visit team considered that a more tailored approach with different reduction targets for different production sectors could also have been very appropriate and effective.⁰⁰⁰⁰

The team further acknowledges the Covenant between the authorities and stakeholders signed in June 2016 (see section 6.2.2.1)⁸⁶ as the currently applicable veterinary national action plan in Belgium, outlining relevant strategic and operational goals.

However, the visit team did not consider the afore-mentioned documents as a truly holistic or comprehensive One Health action plan on AMR and noted that some adaptations to the current organisational and working arrangements of the various bodies involved are necessary to facilitate and more effectively coordinate actions against AMR. In addition, the team did not identify any particular action plan or strategy to address the environmental aspects of AMR.

9.2.1.3 *Monitoring the use of antimicrobials in animals (incl. critically important antimicrobials)*

The visit team was informed on the BelVet-SAC project, the Sanitel-Med database and AB register (see section 4.2.2.1), but also learnt from presentations on various production sector quality assurance schemes which have systems in place for the recording of antibiotic use by their farmer members, that in many cases different schemes are used by farmers in the Flemish and Walloon regions.

⁰⁰⁰⁰ In their response to the draft report, the competent authority noted that data on the use of antibiotics were not available on a sector level at that time. General reduction targets were set with the intention to subsequently break these down into reduction targets for different production sectors. In the meantime, the preparations for the development of an official central database were ongoing.

9.2.1.4 *Activities to promote prudent use of antibiotic in animals*

The visit team recorded the following activities and initiatives to promote prudent use of antibiotic in animals:

- AMCRA's electronic vade-mecum for companion and food-producing animals, freely accessible and funded by Pharma.be (see section 6.2.2.2);
- The prohibition for the pharmaceutical companies to sell antibiotics directly to veterinarians (with a wholesaler or distributor always being placed in between) and the fact that volume-price incentives are not allowed (see section 6.2.2.1);
- Since 2014, a sales tax on veterinary antibiotics (see section 6.2.2.1);
- The Royal Decree of 21 July 2016 introduced the prohibition on the preventive use of critical important antibiotics (CIAs) and defined the conditions for their metaphylactic and curative use (see section 6.2.2.1)^{pppp};
- Belpork, Codiplan, Belbeef and Belplume encourage their members to use antibiotic in optimal way through recommendations and advices concerning antibiotic use;
- The online application Biocheck (see section 6.2.2.5) allows farmers to complete an online questionnaire, receive a biosecurity score, and for this score to be compared between different farms and over time taking different biosecurity risks into account; this tool is currently available for pig and broiler farms and by June 2018 should also be developed for

^{pppp} During a farm visit, the attending veterinarian reported that since the RD on CIA, he had euthanised up to 6 times more veal calves due to unresolved chronic respiratory disease compared to previous year, yet, there were no data available that supported this assertion. The visit team suggested to review production data and investigate possible consequences of the RD on CIA on animal morbidity and mortality.



dairy and beef cattle, veal calves, poultry breeding flocks and laying hen farms^{qqqq};

- Since 1 January 2016 electronic prescriptions for medicated feed are mandatory, which the veterinary authorities believe have facilitated improved controls on the use of medicated feed.

Yet, the team also noticed some weaknesses:

- Some of the stakeholders who have signed the June 2016 Covenant did not make any differentiation between reduced and prudent use of antibiotic (quantitative & qualitative aspects);
- So far, limited attention has been paid to the potential impact on animal health and welfare, and farm profitability and productivity aspects of aiming of such large reductions in antibiotic use over a relatively short period;
- It could have been beneficial for stakeholders (especially for farmers and veterinarians) if specific tools such as benchmarking were already in place when or shortly after these reduction targets were agreed, to enable veterinarians and farmers to compare their prescribing and use patterns to their peers and for the authorities and other stakeholders to identify those critical success or failure factors leading to low or high antibiotic use in animals;
- Some of the agreed objectives under the 2016 Covenant appeared quite vague, general and aspirational or stakeholders had little sense of how some of the stated and agreed actions could be achieved in practice; but also, in some cases particular actions had already been completed before the Convention was signed;
- The treatment of young calves under 1 month of age with veterinary medicines (so also antibiotic) is not required to be recorded if the calf is still on its farm of origin at the time of treatment.

^{qqqq} As there is some delay, the launch of the tool for dairy and beef cattle, veal calves, poultry breeding flocks and laying hen farms is expected by the end of 2018.

9.2.1.5 *Communication and awareness activities on AMR and the prudent use of antimicrobials in animals*

The visit team was informed of the following activities on the prudent use of antibiotic in animals:

- Symposia on the occasion of the European Antibiotic Awareness Day;
- From October to December 2016, FOD VVVL – SPF SPSCAE in collaboration with AMCRA, organised roadshows for veterinarians and farmers to sensitise them on the need to combat AMR;
- AMCRA communication tools;
- AGROFRONT (comprising three farmers' unions in Belgium, Algemeen Boerensyndicaat, Boerenbond and Fédération Wallonne de l'Agriculture) collaborated with other stakeholders and the authorities to provide information and coaching to farmers on monitoring their antibiotic use and to encourage the responsible use of antibiotics;
- The Association régionale de santé et d'identification animale (ARSIA), organises the “*ALTibiotique*” training programme for farmers to use antibiotic less and better and inform them on the alternatives to the use of antibiotics^{rrrr}.

The following weaknesses were recorded:

- The two small animal clinic veterinarians visited were not aware of any particular leaflets, posters or radio advertisements in Belgium on the subjects of AMR or prudent use of antibiotic. They also said that insufficient attention is currently given to the topic of infection prevention and control in the undergraduate veterinary curriculum in Belgium and that they hear more about these topics when attending conferences abroad.

^{rrrr} <http://www.arsia.be/>



As has been successfully used in some other Member States, the visit team considered that some further attention could be given to additional support, supervision and even controls which could be applied in the future to motivate high antibiotic using farmers and high prescribing veterinarians to change their behaviour.

9.2.1.6 Overall conclusion

Belgium does not yet have a truly One Health national action plan on AMR because initiatives on human and veterinary sectors are generally separate and very little attention is currently being given to the environmental aspects of AMR. In this sense, greater cooperation and coordination between the different sectors could be beneficial.

In addition, so far issues related to companion animals have often not been included in the various communication and awareness-raising activities.

Ambitious veterinary antibiotic use reduction targets have been recently agreed with stakeholders, but not all of the expected tools and necessary support elements are in place to achieve these (e.g. benchmarking of prescribing and use of antibiotics, identification of critical success or failure factors and further dissemination of good practices).

9.2.2 Considerations for possible future actions

The visit team suggests the relevant competent authorities to consider the following points in further developing and implementing national policies and strategies on AMR:

- There should be scope for greater and more effective collaboration and cooperation between the human health, veterinary and environmental sectors in order to address the implementation of national AMR policies in a more holistic One Health perspective; a single One Health action plan against AMR may be very useful in that respect;
- It should be beneficial to have within BAPCOC shared discussions between veterinary and human health sectors on issues such as awareness campaigns and infections prevention and control; currently veterinarians are not represented in the dedicated working groups;
- It would be good to have a more integrated analysis and reporting of AMR surveillance and antimicrobial sales and usage trends, between and within both the veterinary and human health sectors;
- Even if setting ambitious antibiotic reduction targets in animals can be a valuable way of effecting change and modifying behaviour concerning the prescription and use of antibiotic, vigilance is required to ensure that these targets do not jeopardise animal health, welfare or the production viability and profitability of farms, especially in case of steep reductions;
- Sector-specific antibiotic use reduction targets have to be proposed because different animal production sectors have a greater or a lesser capacity to more easily reduce antibiotic use without jeopardising animal health, welfare and production parameters;
- On the specific issue of CIAs in animals, the sharing of experiences and treatment approaches between veterinarians in Belgium and other member states is encouraged;
- Necessary supporting tools should be made available to farmers, veterinarians and other stakeholders when antibiotic use reduction targets are established in order to assist their efforts to ensure the reduced and more prudent use of antibiotics and comply with these targets. The tools could encompass the benchmarking of antibiotic prescribing and use, identification of relevant critical success and failure factors contributing to low or high antibiotic use, and identification and dissemination of good practices. Greater emphasis could be given to seeking alternatives to antibiotic, disease prevention, husbandry, possible nutritional supplements and use of slaughterhouse feedback data on lesions detected at slaughter as a feedback and monitoring tool for individual farms in some specific sectors (e.g. pigs and veal calves);
- In addition to the current initiatives which focus to a large extent on the quantitative aspects of reduced antibiotic use in animals, the qualitative aspects concerning prudent use of antibiotic also need due attention. Likewise, attention should be given to the impact of certain trends, such as a reduction in medicated feed use or a rapid and steep reduction in CIA use. As the difference between the reduced and prudent use of antibiotic was not clear for some stakeholders, some further discussions on this issue can be beneficial;



- In order to motivate high antibiotic using farmers and high prescribing veterinarians to modify their behaviour, the provision of additional support, or the organisation of supervision and controls at those levels should be considered. The aspects relevant to AMR and prudent use could be incorporated into official controls performed for other purposes on farms, veterinary practices, and feed mills producing medicated feed;
- Attention should be given to the possibility of further harnessing the influence of food retailers and processors to drive further changes and possibly incentivise farmers towards the reduced and more prudent use of antibiotics;
- More attention should be given to the topics of AMR surveillance and prudent antibiotic use in companion animals (pets and horses);
- There seems to be considerable scope to involve Belgian university veterinary medicine faculties and veterinary nurse training establishments to a greater extent in AMR and prudent use activities and to give greater attention to the topic of infection prevention and control in the undergraduate veterinary curriculum (as well as collaborating with relevant human health counterparts on this topic).

10 DISCUSSION

This reports presents a wide overview on the prudent use of antibiotics in Belgium, the factors influencing this use and what could be done to improve it. As antibiotic resistance is influenced by the human, animal and environmental sectors, we took a One Health perspective and investigated both the human and animal sector. However, we did not cover the environmental sector due to a lack of time and resources.

Since BAPCOC's foundation in 1999, more than 30 different policy measures and interventions have been conducted in the medical sector to improve the prudent use of antibiotics, in addition to several guidelines on antibiotic prescribing. Although the real impact of each intervention is difficult to evaluate, an initial positive effect was suggested by a decline in overall antibiotic use (in DDD per 1000 inhabitants per day) in the first years after BAPCOC's foundation.^{11, 109} However, a lack of further decline in the last decade and the stagnation at a high level (21 DDD per 1000 inhabitants per day in 2017 in the ambulatory sector) indicate that additional or improved strategies should be developed. Our study also revealed that most BAPCOC's budget is allocated to interventions in the hospital sector.⁴⁷¹ This may be explained by the high AMR prevalence and proportion of patients exposed to antibiotic treatment (28% patients in the 2017 PPS) in hospitals.^{39, 140} However antibiotic stewardship is not properly developed in the ambulatory sector, where the bulk of antibiotics are prescribed, nor in nursing homes.

In the veterinary sector, AMCRA and federal agencies, have also developed a number of initiatives and policy measures to improve the use of antibiotics in animals. Most interventions have addressed the sector of food producing animals, in which economic interests are an important leverage for change. In the last decade, a substantial reduction in the amount of antibiotic use (reduction of 16% mg /kg biomass in pharmaceuticals and 67% in premixes between 2001 and 2017). However, so far the sector of companion animals has not received much attention yet. The literature review and the interview of many actors involved in prudent use indicate that other important factors are playing a role in the decision to prescribe or use antibiotics, such as risk avoidance and dealing with uncertainty. A majority of the interventions have so far focused on increasing knowledge and awareness. However,



knowledge does not automatically translate in behaviour change, due to cultural, psychological, social and institutional determinants. Addressing these determinants requires additional strategies.

The marketing activities of the pharmaceutical industry seems to have contributed to a high use of some specific molecules in the past (e.g. moxifloxacin in 2003),⁴⁷² and ECDC also noted that they still have an influence on prescribing behaviour (see section 9.1.1.7). Yet, it was not identified as a determinant in the 20 Belgian studies on antibiotic prescription and use, and their activities were not reported as being currently influential by the experts interviewed (although a question on this aspect was included in the scoping interviews). Indeed many interviewees reported that new ethical codes (in particular Mdeon)^{SSSS} and the current low profitability of antibiotics for the pharmaceutical industry seem to have minimised their influence on the prescribers in the last decade.⁴⁷³

Our research also pointed to rooms for improvement at the policy level, such as the need for recognition of the medical specialties in infectiology and/or medical microbiology and the lack of monitoring of antibiotic prescription for companion animals. The competences with regard to antibiotic prescription and use are shared between different levels in Belgium, and a high number of partners are involved. Until just very recently, there was barely structural concertation between them, which also prevents a One Health approach. BAPCOC was installed as a coordinating body, but it misses the authority to build a national strategy (in a One Health perspective) and decide on resource allocation between the different actors involved.

The main strengths of our study are the One Health approach that involved both medical and veterinarian sectors, the involvement of a high number of stakeholders and actors (about 57) from both sectors through in-depth interviews and stakeholder meetings, the broad literature reviews in both sectors, the in-depth analysis of Belgian antibiotic use data, the inventory of all Belgian interventions, and the use of qualitative methods to produce a systems map, validated by Belgian actors, to develop the recommendations.

We also benefited from a very valuable personal contribution from a number of field actors to understand the system and refine the recommendations.

Our study has also a number of limitations. First, due to limited time and resources, we limited our scope to the prudent use of antibiotics and did not cover the following other issues involved in AMR: environmental health, activities to limit AMR spread such as infection control in hospitals, and the development of new antibiotics. We did not describe AMR data as these are widely available in other reports (e.g. Sciensano).^{39, 140, 474} We mostly addressed the overall antibiotic use and not the specific issue of some antibiotic classes (with the exception of quinolones and amoxicillin-clavulanate), nor did we describe the problem of specific AMR problems in hospital acquired infections (such as MRSA and carbapenem resistance), although these may represent a burning challenge for Belgian practitioners. We did not involve dentists, nurses, veterinarians in companion animals among consulted stakeholders.

Another limitation is the difficulty to find robust evidence on the effectiveness of policy measures and interventions from other settings. Although we found several systematic reviews on specific interventions, the lack of standards and the diversity of interventions (differing sometimes by hospital) limited the credibility of meta-analyses and their inference to other contexts. The evaluations involved different methodologies and different outcomes, and the results were regularly conflicting. We also understood that the solutions are context-specific, simply copying solutions from abroad is certainly no guarantee for success. Therefore, we opted to use the results of evaluations conducted in Belgium and the consultation of stakeholders, rather than performing a comprehensive international comparison.

Based on our findings, draft proposals for further improvement of the situation have been presented and discussed in several meetings with relevant stakeholders. Based on their input, the recommendations have been further refined. They are presented in the next section.

SSSS Ethical Health Platform <https://www.mdeon.be/en/>



11 HOW CAN THE SITUATION BE IMPROVED^{tttt}?

Based on what we learnt from the international literature, the policy documents, the national and international reports, the analysis of reimbursement data and the broad consultation of stakeholders, we recommend the following in order to promote the prudent use of antibiotics in the Belgian human and veterinary sector, so that antibacterial resistance can be reduced. We opted not to give any priority ranking to the various recommendations as the future impact of each strategy is currently unknown. Only for the convenience of the reader, we numbered the recommendations:

11.1 Develop a national One Health AMR action plan

Belgium was one of the first European countries to implement a national antibiotic policy coordinating commission. The work and dedication demonstrated so far by the Belgian Antibiotic Policy Coordination Commission (BAPCOC) are considerable.

A national One Health AMR action plan countering AMR should be developed, together with all involved parties, i.e. according to the One Health approach. The action plan should be evaluated on a regular basis, so that gaps or deficiencies can be identified and so that it can be adjusted where indicated. Effective leadership should facilitate the inclusive participation and engagement of relevant stakeholders including national and regional ministries/public services, the medical and veterinary professions, the pharmacists, research and academic institutions (including the social and behavioural sciences), agricultural organisations, and the food and pharmaceutical industries.⁴⁷⁵ Collaboration with other partners at the European and international level should be ensured on AMR issues that go beyond the national context.

The ECDC country visit team (see chapter 9) already suggested the development of a national action plan on AMR. According to the ECDC team, it should be implemented in a **multi-disciplinary way**, it should include a strong infection prevention and control component and a tangible presence from the relevant ministries. Its activities should not be limited to antibiotic policy alone.

Tackling the threat of AMR requires a **multisector approach**, referred to as One Health.⁴⁷⁶ In the One Health AMR action plan it should be ensured that the human, veterinary and environmental **sectors collaborate intensively**, for instance to avoid the current situation where the sectors are working in parallel (see the systems map, which clearly illustrate the human and veterinary clusters having little or no variables in common (see chapter 7). Currently, the **various responsibilities with regard to prudent antibiotic use and AMR are shared out** to (several persons working within) several institutions (see chapter 3). It is thus very important to ensure **coordination of the actions** taken by the many involved partners (e.g. BAPCOC, the federal public services, the agencies of the federated entities, Sciensano, RIZIV – INAMI, FAGG – AFMPS, FAVV – AFSCA, AMCRA, academic institutions).

To effectively curb AMR, **strong leadership** is essential.⁷⁶ **High level experts** (incl. medical doctors with expertise in infectious diseases and veterinary doctors) should be involved because a core group of scientists is needed to address all the AMR tasks and to support the implementation of the activities stipulated in the One Health AMR action plan. They should ensure a strong technical expertise and should receive an appropriate remuneration for their work. The current situation with everybody involved participating on a voluntary basis (with the exception of the support team), adversely affects the persistence and continuity of BAPCOC's activities (see chapter 7).

^{tttt} The KCE has sole responsibility for the recommendations.



Sufficient and stable resources are needed to ensure that initiatives can be taken in all sectors but also between the different sectors. These resources must be readily available and should be provided **collectively** by the human, veterinary and environmental sectors.

The One Health AMR action plan should also address the development, implementation and evaluation of **interventions** that promote the prudent use of antibiotics and tackle AMR. An inventory of all implemented antibiotic use/AMR interventions should be made and kept up-to-date; the inventory should be made accessible to all so that actors involved can learn from each other (by analogy with the POP database^{uuuu}).

In addition, in the action plan it should be defined which data are requisite for decision making, who should compile them and how they should be shared. A **One Health antibiotic use and AMR report**, comprising data from all involved sectors should be published on a yearly basis; the DANMAP report can be used as a source of inspiration (<https://www.danmap.org/>).⁴²⁷

In the other recommendations (11.2-11.21) more items are described that should be included in the action plan.

11.2 Strengthen antibiotic stewardship in acute care hospitals

Since 2007, multidisciplinary antibiotic management teams (AMT) are mandatory in all acute care hospitals and large (i.e. 150 beds or more) chronic care hospitals. Their legal framework and funding (in 2018: € 4 433 298) have been established in Royal decrees.^{275, 277, 278}

As said before, the legislation on the antibiotic management teams has some important shortcomings (e.g. **minimal human resources** nor targets defined). Moreover, hospitals not performing well, are not forced to improve the situation; there are no consequences whether or not improvements are realised. Last but not least, the general public is not aware which hospital performs well and which not.¹¹⁸ The One Health AMR action plan should

include initiatives (among others at the **legislative level**) to improve that situation. But also, hospital managers should **give account for the AMT funds** they receive. At present, there are no data on the actual use of the AMT funding within hospitals.²⁴

Initiatives in certain hospitals that **increase the authority of the antibiotic management teams** and that facilitate that hospital policies are **implemented at the ward level** (e.g. Post-Antibiotic Prescription Review, Automatic stop order) should be further evaluated. If proven effective, it should be assessed how they can be adopted in other hospitals. Stakeholders indicated that antibiotic management teams could benefit from more support from the national level (currently BAPCOC) in terms of concrete projects (e.g. sharing of 'success stories') and quality improvement initiatives (see chapter 7).

According to the stakeholders, the prudent use of antibiotics in the wards can be improved substantially by increasing the involvement of specialists **in infectiology/medical microbiology in the wards**, so that they can give technical advice on specific cases. Yet, this requires a system to remunerate this advice (see chapter 7). Likewise, the role of hospital pharmacists in the wards regarding the prudent use of antibiotics should be reinforced, by analogy with the model of nurses of the infection control teams who are on the job and who give concrete advice to the specialists in the various hospital wards. Sufficient resources should be made available to also realise that in smaller hospitals.

To preserve last-line antibiotics, **barriers should be reinforced** in the hospitals' prescription system (e.g. reinforce the system that prescription of certain broad-spectrum antibiotics are restricted to specific medical specialties or for specific indications).

The **quality improvement projects** that are implemented in hospitals (e.g. Pay for Performance, VIP², external quality accreditation; see chapter 6) should systematically include a number of indicators related to the prudent use of antibiotics.

^{uuuu} The EUnetHTA Planned and Ongoing Projects (POP) database allows HTA agencies to share information with each other on planned, ongoing or recently

published projects conducted at the individual agency. The aim of the database is to reduce duplication and facilitate collaboration among HTA agencies. (<https://www.eunetha.eu/pop-database/>)



11.3 Roll out local antibiotic stewardship teams in the ambulatory sector

Currently, the bulk of antibiotics in Belgium are prescribed in ambulatory care, as is the case in many high-income countries.⁴⁷⁵ Available AMR data reflect mostly the hospital sector. Yet there are only limited antibiotic stewardship initiatives in this sector. In addition, the greater part of BAPCOC's financial resources are allocated to actions in the hospital sector (see chapter 3).

Local antibiotic stewardship teams for ambulatory care should be developed and rolled out over the whole country (e.g. within the current structure and organisation of the Lokale Kwaliteitsgroepen (LOKs) and Groupe Local d'Évaluation Médicale (GLEMs)). The stewardship teams could be moderated by local general practitioners (GPs) who are regularly updated (e.g. yearly) in antibiotic stewardship. The local antibiotic stewardship teams should not only include GPs, but also **pharmacists** and specialists **in infectiology/medical microbiology from the local hospitals** (in order to ensure exchange of information and expertise). In the One Health AMR action plan the overall strategy should be defined.

The local antibiotic stewardship teams should have access to anonymised prescription data of the GPs working in their catchment area and with a minimal delay so that they can be reviewed among peers. They should also have access to the AMR data that reflect the local epidemiology at ambulatory level (community acquired infections).

The local antibiotic stewardship teams should invite the local GPs on a regular basis, to **provide continuous education** (e.g. on the recent AMR situation), to discuss their **prescription behaviour** and possible interventions, to improve their **communication skills** with patients, and to share experiences, lessons learnt etc. encountered in their daily practice. This could be encouraged by including it in the current accreditation system.

The members of the local antibiotic stewardship teams should be available and able to provide ad-hoc advice to their peers in case they need rapid advice on e.g. the type, dose and/or duration of an antibiotic for a specific patient; this could be organised through e.g. an on-call system or a mobile messenger service adapted to health care services (e.g. Pandalab

(<https://www.pandalab.fr/>) in France). In addition, peer **support** and support from specialists in infectiology/medical microbiology from the local hospitals should be provided.

The activities of the local antibiotic stewardship teams and referent specialists should be **funded**.

Similar initiatives should be taken for medical specialists working in the ambulatory sector (e.g. dermatologists, pneumologists, ENT specialists, paediatricians) as well as for dentists.

Close collaboration between the stewardship initiatives taken in the hospitals, ambulatory care and nursing homes (cf. infra) of the same area should ensure an integrated approach in the three sectors. Inspiration can be found in Sweden, where different health care professionals from general practice, hospital medicine and long-term care are collaborating closely in local STRAMA (Swedish program to combat AMR) groups. The STRAMA groups facilitate coordination and knowledge transfer between all levels of care locally whilst coordinating with the national STRAMA steering group and the Swedish public health agency. In this way they are acting as a mechanism to adapt national initiatives to local settings.⁴⁷⁵

11.4 Develop antibiotic stewardship in nursing homes

There is a substantial problem of antimicrobial resistance in nursing homes. In addition, there are currently several barriers to antibiotic stewardship in nursing homes: the legislation describing the role of nursing homes' 'coordinating and advising physicians', does not specify a precise task in terms of antibiotic policy,³⁰⁵ and many GPs take care of the residents within a single nursing home as every nursing home resident can choose his own GP.³⁰⁶

In order to improve the prudent use of antibiotics and to address the problem of AMR in nursing homes, antibiotic stewardship should be further developed in these facilities. This recommendation is in line with the European guidelines for the prudent use of antimicrobials in human medicine, issued in 2017 by the European Commission.³



The role of the coordinating and advising physician needs to be adjusted for that purpose. The data on the prescription behaviour of GPs caring for nursing home residents and on AMR in nursing homes can contribute to develop locally relevant activities leading to a more prudent use of antibiotics. In addition, the results of the pilot project in four nursing home consortia, the set of recommendations developed by a 2018 FOD VVVL – SPF SPSCAE report and the results of the ECDC-coordinated point prevalence surveys in nursing homes (the so-called HALT surveys, see section 4.2.1) could be used as a basis for developing stewardship action plans for nursing homes.³⁰⁸

The antibiotic stewardship initiatives in the nursing homes should be taken in **close collaboration with the antibiotic stewardship teams of the local or regional hospitals** (e.g. to set up initiatives to prevent the spread of resistant bacteria when nursing home residents' illness requires hospital admission) and in close collaboration with the **local ambulatory antibiotic stewardship teams** (e.g. to set up initiatives to prevent the spread of resistant bacteria from nursing home residents and their relatives and friends) to obtain an integrated approach. In addition, peer support and support from specialists in infectiology/medical microbiology from the local hospitals should be provided.

11.5 Improve the professional education on prudent antibiotic prescription and use, and develop and implement interventions targeting psychological, social and institutional determinants of behavioural change

*According to the stakeholders, the **academic training** on the prudent prescription and use of antibiotics presents gaps due to the fragmentation of the infectiology teaching base over different subdisciplines, which prevents consistency. This is a result of the fact that infectiology is not recognised yet as a separate discipline (cf. infra). Currently, there is no system of mandatory **continuous education** on antibiotic prescription and AMR for prescribers. There is no requirement that quality circles (LOK – GLEM) focus on the topic of prudent antibiotic prescription nor that practitioners attend these sessions.*

In order to improve the prudent use of antibiotics and to address the problem of AMR in all sectors, the quality of the training on prudent antibiotic prescription and use should be improved. It was also reported to the ECDC country visit team (see chapter 9) that many GPs and other clinicians lack knowledge on the mode of action of different antibiotics, their indication and use. For example, the ECDC country visit team recorded anecdotal evidence that doctors overprescribe quinolones for acute, uncomplicated urinary tract infections, amoxicillin-clavulanate for simple skin infections, amoxicillin rather than penicillin V for tonsillitis, or combinations of oral and topical antibiotics simultaneously.⁷⁶

In order to improve the knowledge on the prudent prescription of antibiotics and AMR, the continuous education should include a **mandatory yearly or biannual** module on these topics, as recommended by the ECDC country visit team.⁷⁶ The observation that physicians partly maintain antibiotic prescribing habits of the past as they age,¹⁷⁸ is an additional argument for the mandatory continuous training in these topics.

Last but not least, training sessions should be regarded as an excellent opportunity for knowledge exchange between the veterinary and human sectors.



Knowledge on itself (realised through among others training, peer education, guidelines, and awareness campaigns) is an essential, yet insufficient condition for behavioural change. It is no coincidence that knowledge is also the easiest to influence and/or to adjust.⁴³³

The One Health AMR action plan should thus include interventions targeting psychological, social and institutional determinants of behavioural change as well. Improvement strategies only have a chance of success when all types of barriers are targeted.²⁶⁴ For this purpose, collaboration with the Evidence Based Practice (EBP)^{www} implementation cell should be envisaged.

11.6 Recognise medical microbiology and infectiology as medical specialty and provide remuneration for their advice

Specialists with appropriate expertise and training about antibiotics and AMR, such as those in infectious diseases and medical microbiology, as well as laboratories of medical microbiology, are essential to ensure appropriate treatment of infections, appropriate use of antibiotics and support for antibiotic stewardship programmes.⁷⁶ These medical specialties are mentioned in the royal decree (RD) of 2008 stipulating the composition of the antibiotic management teams in hospitals, and the vast majority of EU countries have already recognised them officially as medical specialty. Yet the approval of infectiology and medical microbiology as medical specialty in Belgium is still outstanding anno 2019.²⁷⁸

As was also suggested by the ECDC country visit team (see chapter 9), infectious disease specialisation should be **legally recognised** and their advice should be eligible for **remuneration**.⁷⁶ These specialists should not only be involved in the antibiotic stewardship programmes in the hospitals, the ambulatory sector and the nursing homes, but also in the training and

continuous medical education of medical doctors and dentists. They should be available in the hospital wards for onsite consultation as well.

11.7 Improve the availability of old/narrow spectrum antibiotics

A vital component in the battle against AMR is access to the right antibacterial product. Yet, sometimes (old, narrow spectrum) antibiotics are not (longer) available on the market, or temporarily unavailable or not available in the correct dosage or formulation suitable for children (see chapter 8). The inadequate availability of certain antibiotics has a serious impact on antibiotic prescribing: prescribers may be forced to replace them by less optimal, often broad-spectrum antibiotics. The alternatives may be less effective, may have more adverse effects, and may be more prone to drive the selection of resistance.⁴⁵⁹ Hence, the lack of availability of certain antibiotics is a threat to antibiotic stewardship.

The One Health AMR action plan should include an appropriate approach for this problem. One should identify key antibiotics vulnerable to shortages and price increases and investigate together with FAGG – AFMPS how the **availability of old/narrow spectrum antibiotics on the Belgian market can be improved** and how therapeutic alternatives can be made available when certain antibiotics are removed from the market. As this problem is not confined to Belgium and the actors involved (among others pharmaceutical companies) are operating in an international context, a European approach will be indicated (e.g. through a multidisciplinary international taskforce, as is suggested by others).⁴⁶⁰ Negotiations should also ensure high quality of medicines, continued production, a reasonable stock policy, and avoid dependence on a single supplier.⁴⁶⁰

^{www} The EBP Network, initiated by the minister of Social Affairs and Public Health in 2016, aims at coordinating all federal initiatives related to Evidence Based Practice (EBP) in Belgium. In this network, Ebpracticenet (www.ebpnet.be) disseminates guidelines and other EBP products by offering a central, unique and dedicated distribution platform for the spreading of EBP information in

Belgium. Ebpracticenet also takes up the role of implementation cell. The goal of the implementation cell is to stimulate the real practice use of guidelines and other EBP products, and to change the behaviour of healthcare professionals and patients. Currently this network focuses on primary care, but extension to secondary care will be considered in the future.



In addition, the One Health AMR action plan should describe how prescribers can be informed pro-actively that a temporary supply problem occurs, but also when it has been solved; this should be done in close collaboration with FAGG – AFMPS.

11.8 Put into practice the delivery of the exact number of antibiotic tablets in pharmacies open to the public

Packages of antibiotics available on the Belgian market are often larger than what is needed for one treatment, which increases the risk of keeping leftovers at home and of subsequent self-medication (see chapter 8). Self-medication with antibiotics is inappropriate because of the possibility of an unnecessary therapy, incorrect choice of antibiotics, of insufficient dosages, or of inappropriate duration.²³⁸ But even when leftover antibiotics are discarded, they add to the problem of environmental pollution. Therefore, unlike most other drugs that in case of incorrect use may simply pose a risk to the particular patient, the inappropriate use of antibiotics adds to the global risk of increased antibacterial resistance.²³⁰

An effective way of **preventing self-medication with antibiotics** is the prevention of leftovers from prescribed courses. This can easily be implemented by the **dispensation of the exact number of antibiotic tablets in pharmacies through fractionation**, as is already the case in the UK, the Netherlands, US, Japan, Israel and the Czech Republic.^{217, 230, 238}

Since 2006, pharmacists working in pharmacies open to the public are **authorized** to fractionate medicine packages, provided that certain conditions are met, one of them perfectly addressing the problem outlined above: ‘there is no adequate primary package size of the medicinal product, licensed and marketed in Belgium, for the duration of the treatment for which it is prescribed’.¹²⁶

Upon inquiry with FAGG – AFMPS it appeared that there are still barriers to be cleared in order to extend the current fractionation activities to e.g. antibiotics: prices and reimbursement rules have to be adopted (these are set now per package and not per unit), computer systems used by pharmacists have to be adapted (which currently only record the delivery of a box of medicines to one patient and not to several) and prescribers have to be informed. With regard to the financial aspects, the billing rule for

nursing home residents issued in 2015 can be a source of inspiration (see chapter 8). In the interest of the patient, the price should be defined per unit. If fractionation of medicines is indeed extended to e.g. antibiotics, FAGG – AFMPS will also have to adapt its supervision (e.g. the expiry date, the patient leaflet). (FAGG – AFMPS, *personal communication*)

11.9 Improve the compliance with evidence-based prescription guidelines

The prudent prescription of antibiotics starts with evidence-based guidelines, which clearly mention for each indication a first and second choice antibacterial agent, dose, posology and duration. Yet, some stakeholders reported that the visibility, the regular updates and the alignment of the different guidelines could be improved and thus enhance compliance. For instance, BAPCOC has published a guideline on the prudent use of antibiotics in the ambulatory sector (last version 2012, update expected in 2019), but in summer 2017 RIZIV – INAMI spread the report of a consensus meeting (held in June 2016) on the use of antibiotics in children in ambulatory care, which leads to confusion in the sector (and among stakeholders). Anno 2019, there is still no guideline on the prudent use of antibiotics for dentists. In addition, the impact of the antibiotic guidelines alone is limited in daily practice by a number of factors described earlier. In particular, their dissemination and their subsequent availability at the point of care is too often limited, they meet opposition and distrust from the clinician side, and in hospital care they need to be adapted to the local health care settings, drug formularies and resistance patterns.^{171, 337}

In the One Health AMR action plan it should be stipulated how the **development and update** of guidelines should be coordinated for the various sectors involved and how it can be ensured that they are adapted to the different target groups of professionals. These guidelines should be used in the curriculum and continuous training of physicians, dentists, pharmacists and nurses. Access and visibility must be improved, and free access to electronic versions should be ensured (through e.g. funding of the



IGGI guide^{www}) In that respect, the current digitization of health care ('e-health') brings about important opportunities: e.g. accessibility to **decision-making tools** for therapies in accordance with national guidance or warnings in the event of inappropriate prescription, **E-prescribing** can be linked to national guidelines (through e.g. pop-up windows reminding the clinician what the first choice antibiotic is and why).

11.10 Make use of the (future) mandatory implementation of e-prescribing to improve the prudent prescription of antibiotics

E-prescription will become mandatory on 1 January 2020.⁴⁷⁷ It presents many opportunities to improve prudent prescription and to inform prescribers on their prescription behaviour.

Information on the **indication** (type of infection) for each antibiotic prescription should be incorporated in the e-prescription module, so that criteria for prudent use can be assessed, allowing to improve monitoring and feedback on the prescription of antibiotics. In this way, incentives for prudent prescribers can be envisaged.

In addition, **decision-making tools** for therapies, including the prudent use of antibiotics, should be developed in accordance with national guidelines. They should provide warnings in the event of inappropriate prescription, and be made accessible, e.g. through a linkage between e-prescribing and national guidelines or through a linkage of decision-making tools with the Electronic Medical Record (EMR) as foreseen in the EBP network. Likewise, linkage to regulations and forms (e.g. prescription of fluoroquinolones under Chapter IV) should be included.

The One Health AMR action plan should address how e-prescription may lead to faster feedback of prescribing practices to GPs and other prescribers;

this should be done in close collaboration with the respective departments of RIZIV – INAMI.

11.11 Consider taking structural measures to improve the prudent prescription and use of antibiotics

The international literature and the consulted experts suggested several structural measures which may improve the prudent prescription and use of antibiotics.^{163-165, 206, 214, 215}

The One Health AMR action plan should comprise an approach to evaluate which structural measures can improve the prescription and use of antibiotics in **the Belgian context**, based on scientific evidence. This should be done based on scientific evidence and in close collaboration with the stakeholders.

11.12 Perform a health technology assessment on point-of-care testing for the diagnosis of infectious diseases in the Belgian ambulatory care context

In the ambulatory sector the treatment of infectious diseases (e.g. upper respiratory tract infections) is most often empirical (i.e. based on a case history, clinical examination and previous experience of the healthcare provider), which is of poor accuracy in identifying the likely aetiology and thus when antibiotics are required.⁴⁷⁸ However, most respiratory tract infections in the ambulatory sector are from viral origin. Usual laboratory-based tests, which are sensitive, result in too long delays to guide the immediate prescription. Point-of-care testing, such as C-reactive protein (CRP) test or procalcitonin, may assist the clinician to assess the likelihood of a serious bacterial infection versus a less severe bacterial or viral infection, and the results may be obtained in a few minutes. In clinical trials

^{www} IGGI: 'Infectiologiegids - Guide d'Infectiologie', developed by the Belgian Society for Infectiology and Clinical Microbiology (BVIKM – SBIMC) with partial support from BAPCOC. Hospitals that want to register for this guideline

have to pay in proportion to their size (i.e. € 2 420/year for hospitals up to 400 beds, €4 235/year for hospitals from 401 to 800 beds and € 6 050/year for hospitals with more than 800 beds).



in other settings, the use of CRP and procalcitonin lowered significantly the rate of antibiotic prescribing.³²⁹

The One Health AMR action plan should comprise a cost-effectiveness evaluation on point-of-care testing in the diagnosis of infectious diseases in ambulatory care in Belgium and an assessment whether it is desirable to reimburse them.

11.13 Stimulate behavioural change among the general public as well as the prescribers towards more prudent use of antibiotics

So far, the national public awareness campaigns on the prudent use of antibiotics included different communication strategies such as posters, advertising in media, brochures, TV spots, bags for pharmacies, and direct mailing (see chapter 6). However, as said above awareness alone is not sufficient to change behaviour.⁴³³ In addition, despite high amounts of resources invested in awareness campaigns, only a limited impact of the last campaigns has been observed.³¹⁶ In addition, the international literature shows that formal education, guidelines and concerns about emerging resistance seem to have minor influence on antibiotic prescribing.^{479, 480}

Sensitisation campaigns should be better targeted and should follow the **One Health approach**, e.g. informing pet owners on the transmission of (resistant) bacteria from their pet to themselves (and the other way around) and their relatives in case of (too) close contact. Sickness funds and patient associations can play a supporting role in these campaigns.

The campaigns should also be **directed to groups that need adapted messages**: e.g. nursing home residents and staff, lower socio-economic groups and citizens who do not master the national languages (see Chapter 5). Differences in terms of health literacy should be taken into account when targeting various groups. Communication teams with special expertise in contacting these groups should therefore be consulted.

Cultural barriers with regard to the prescription and use of antibiotics should be taken into account when organising sensitisation campaigns: e.g. uncertainty avoidance, paternalism, attitude towards self-healing mechanisms.

In order to improve the awareness on AMR and the importance of the prudent use of antibiotics as early as possible, school children should be further targeted as well and **various communication channels** should be used: e.g. social media, local radio stations, popular TV shows not only on the national TV channels, but also on commercial channels and TV channels frequently watched by citizens from non-Belgian origin.

11.14 Strengthen veterinarians' counselling role

Veterinarians earn their income through consultations (farm visits) and the sale of medication; the latter is an important part of the veterinarian's income.⁵¹ Currently, veterinarians' advisory role is quite limited, in the sense that veterinarians have the impression that most farmers are not willing to pay for veterinary counselling.⁵¹ This may in part be explained (at least in pig farming) by the strong position of feed mill companies, which provide "free" veterinary advice.⁴⁸¹

In order to make the improvement of biosecurity (cf. infra) at farms a priority, **veterinarians' counselling role should be strengthened**. Counselling on herd management strategies should be an important part of their professional role, contributing to their revenues. This is only realistic if farmers are willing to **pay for counselling**. This could e.g. be realised through training cheques (e.g. 'opleidingscheques'/'chèque-formation') or be part of the innovation wallet of small and medium-sized enterprises (e.g. 'KMO portefeuille'). Alternatively, a number of (pre-)paid veterinary visits could be made mandatory in the context of a herd health plan. In this way, the one-to-one relationship between a contracted herd veterinarian and the farmer can be enhanced. In the One Health AMR action plan it should be assessed whether incentives should be given to encourage farmers who take up a stewardship relationship with a veterinarian or advisor, who define a herd health plan and who set targets related to antibiotics use in an action plan together with a veterinarian or advisor.

Veterinarians' counselling role and the **one-to-one relationship between contracted herd veterinarians and farmers** should also be enhanced through legislative work: in the legislation on farm guidance, a health plan and plan of action (with targets regarding antibiotics use) could be added as a condition for farm guidance. This is also recommended by AMCRA.⁴⁸² In addition, the prescription and delivery of antibiotics could be made an



exception in the description of the role of the substitute veterinarian in the RD of 10/04/2000 on farm guidance,⁵⁵ in this way the herd veterinarian can keep the overview on the total use of antimicrobials as he provides all antimicrobials for an animal group, with the exception of emergency cases.

11.15 Change prescribing behaviour of high antibiotic prescribers

With the introduction of SANITEL-MED in 2017 the monitoring of antibiotic prescription and use in food producing animals has been installed. The SANITEL-MED register is developed to measure antibiotic use at farm level. Importantly, this comprises individual feedback (including benchmarking) to the farms in the format of two reports a year for every Belgian farm. SANITEL-MED allows the identification of high prescribers. There is currently no monitoring of antibiotic use, nor prescription in the sector of companion animals. Hence, among small animal veterinary practices high prescribers cannot be identified so far.

The One Health AMR action plan should comprise a strategy to identify and monitor high antibiotic prescribers in order to change their prescribing behaviour. Yet, **feedback and benchmarking** are essential but not sufficient: additional **support** and **supervision to change prescribing behaviour** should be provided as well. If this does not help, sanctioning of high antibiotic prescribers (e.g. by the withdrawal of their right to dispense antibiotics) should be considered.

Especially in the pet sector, there are more initiatives needed to realise this. Registration of the prescription and use of antibiotics, should also include information on the indication (e.g. type of infection) and the case-mix of the veterinarian's clientele. A registration system for antibiotic use in companion animals is challenging because the exact number of companion animals (which is the denominator) is unknown. However, pilots could be considered for specific animal species (e.g. dogs and horses for which identification and registration is mandatory) or specific contexts (e.g. kennels and nurseries of small animals) for which exact numbers are known.^{483, 484}

11.16 Monitor and stimulate research on antibiotic use and AMR in the sector of companion animals

From the Household budget survey 2013 we learn that in Belgium about 20% of the households take care of at least one dog, 27% keeps at least one cat and 3% has at least one horse.⁴⁸⁵ Yet, so far the matter of prudent prescription and use of antibiotics and the battle against AMR in companion animals has received little attention in the international scientific literature.

In recent years, AMCRA developed guidelines (e-vademecum) on the prudent use of antibiotics in dogs, cats and horses. But it is unclear to what extent the e-vademecum is actually used by veterinarians.

Within the frame of the One Health AMR action plan it should be investigated how the monitoring of antibiotic use and the surveillance of AMR in companion animals can be realised. Inspiration for this initiative can be found in Denmark, where all prescriptions of antibiotics in livestock and companion animals are recorded in the national database VetStat.⁴²⁷

In addition, in the One Health AMR action plan it should be stipulated that research projects investigating different aspects of antibiotic prescription and use in companion animals (e.g. determinants of antibiotic prescription, barriers to prudent antibiotic use, and transmission of AMR between pets and humans and vice versa) should be stimulated. Last but not least, it should also be investigated how the use of the e-vademecum can be incentivised.



11.17 Stimulate biosecurity improvements as an alternative to antibiotic use

Improved biosecurity (e.g. changes in attitudes, work habits, infrastructure) is beneficial to animal health and welfare, antibiotic reduction and production results.^{258, 409, 422, 486} For example, in an intervention study it was observed that the implementation of optimization of herd management, biosecurity status, and vaccination strategy as a team effort of the farmer together with experts resulted in significant reductions in antibiotic use, while they also had a positive impact on the production results.⁴⁰⁹

For the decrease in antibiotic use a mind shift among farmers is essential: antibiotics should be perceived as a therapeutic solution in case of clinical symptoms of an infection.⁴⁸² Therefore farmers should be well informed about ways to keep animals healthy. Biosecurity measures are often very cheap. They are often more about **attitude and small procedure changes**. Farmers need to be **informed and/or trained** (e.g. during farmers' training programs) about the advantages and importance of healthy animals, the importance of biosecurity to keep them healthy, and the use of antibiotics only as last resort, coupled to the threat of antimicrobial resistance. This could be done by means of a kind of accreditation system.

Develop a licence to administer antibiotic products, not one-off, but with mandatory regular updates (e.g. every 5 years) to keep farmers' knowledge up to date (similar to the phyto licence^{xxxx}). The idea is that a stock of antibiotic products at the farm should be a right that farmers acquire through training, through the presence of a health plan, etc.

Finance additional support, coaching and supervision by veterinarians and independent experts to change farmers' behaviour, especially in farms with high antibiotic use. In addition, it is important to support local groups of farmers and veterinarians meeting regularly to exchange information and experience, and where critical success and failure factors are identified and further disseminated so that good practices can be established.

11.18 Enforce compliance with the legislation on animal welfare

Quite some legislative work has been done in recent years to protect animal welfare. Yet, out of economic interest, exceptions have become the rule, jeopardizing animal health and leading to an increased need for antibiotics. For example, the Council Directive of 18 December 2008 lays down minimum standards for the protection of pigs. More precisely, it imposes a minimum weaning age of 28 days, except for farms with specialised housing which are allowed to wean piglets at 21 days.⁴⁸⁷ Because the sow can be inseminated earlier resulting in more piglets per year, the exception in the law has now become common practice in Belgium, while in a natural setting weaning is a gradual process and the average weaning age is about 17 weeks.^{488, 489} Abrupt weaning at 4 weeks or earlier causes considerable stress for piglets (separation from the sow, change in diet, moving to an unfamiliar barn mixed with unfamiliar pen mates),⁴⁸⁹ leading to growth depression and diarrhoea due to a reduced feed intake and an impaired intestinal tract.^{490, 491} Antibiotics are often used to control post-weaning diarrhoea.⁴⁹² Last but not least, at this young age piglets are also prone to infections because of immaturity of the intestinal immune system,⁴⁹³ leading again to the need for antibiotics. Likewise, legislation stipulates maximum stocking density per animal species (e.g. the Council Directive 2008/120/EC of 18 December 2008 for pigs⁴⁸⁷ and the Council Directive 2007/43/EC laying down minimum rules for the protection of chickens kept for meat production⁴⁹⁴) as there is an important association between stocking density and the animals' health and wellbeing.²⁵⁵ A too high stocking density has a deleterious effect on animal health, resulting in infection pressure and by consequence antibiotic use.⁴⁸²

^{xxxx} A phyto licence is a certificate from the federal government that indicates that a professional user, distributor or information officer can deal correctly with

plant protection products and additives. Through the obligatory continuous licensees remain informed of the developments concerning crop protection. (see also <https://fytoweb.be/nl/fytolicensing/gids>)



It is clear from the examples above that when animal welfare is taken seriously, animal health will benefit and antibiotics are less needed. Therefore **strict observance of legislation on animal welfare** (e.g. regarding the legal minimum weaning age for piglets, minimum age for transport, maximum stocking density) is very important.

In addition, **alternatives** to infeed antibiotics should be sought, other weaning systems developed (e.g. gradual weaning) and feeding programs and nutritional strategies further optimised as a means for controlling problems associated with the weaning transition without using antibiotics.^{488, 489, 493}

11.19 Make the use of antibiotics as means to intensify animal production superfluous

Some farmers still consider antibiotics as an essential link in the chain of production optimisation (e.g. metaphylactic use of antibiotics to prevent disease in the whole herd, antibiotics to treat diarrhoea in weaned piglets because they are weaned too early). However, recent studies indicated that it is feasible to reduce antibiotic usage without jeopardizing production parameters.^{409, 421, 422}

In order to have a durable husbandry, **structural measures** should be taken to stop this race to the bottom. In essence, the consumer price for animal products is too low for animal husbandry to be profitable. As long as consumers are not prepared to pay more for animal products, we keep flogging a dead horse. Measures should be taken to make sure farmers get a decent price for their products.

In addition, the One Health AMR action plan should address how one can push for a level playing field in the international market of animal products. European/international rules for minimum hygiene and biosecurity standards are needed in case of export. This could avoid the competition with farmers from abroad who can sell at lower prices because they do not have to obey the same constraining rules.

11.20 Avoid self-medication by minimizing stocks at farms and by adjusting package sizes

Veterinarians can leave a stock of veterinary medicines for follow-up treatment of up to three weeks at farms that do not have a contract for farm guidance and even up to two months at farms with such a contract (see chapter 3).^{55, 57} This stock of medicines includes antibiotics. Yet, there is no antibiotic treatment that takes as long as two months in the veterinary setting. As is sufficiently known, leftovers of antibiotics give way to self-medication.

Small package sizes (sometimes licenced) and uni-doses of antibiotics are seldom commercially available. Hence, veterinarians are often not able to provide the exact volume necessary for the treatment because of packages being too large and because of the legal restrictions on and practical difficulties with fractionation (e.g. availability of a package leaflet together with each fraction).

In order to avoid leftovers of antibiotics at farms, the legislation with regard to the maximum stock veterinarians can deliver at farms for follow-up treatment by the farmer should be adapted, by making an exception for antibiotics.^{55, 57} The **maximum stock of antibiotics should be limited to the duration of the treatment** as defined in the product specifications. In addition, a stock of antibiotics at farms should be made conditional to e.g. the presence of a health plan, coupled to a minimum number of (remunerated) meetings with the herd veterinarian (e.g. 4 times a year).

Alternatively, the size of the antibiotic stocks at farms could be made proportional to the number of animals. This is already the case in the Netherlands, where the stock of first-choice antibiotics can be maximum 15% of the animals at risk on the farm. For second-choice antibiotics the conditions are more strict (e.g. farmers can only administer second-choice antibiotics after contacting a veterinarian) and linked to the farm's health plan.⁴⁹⁵



Within the frame of the One Health AMR action plan it should be investigated how fractionation of antibiotic products can be realised in a safe way and/or whether it is possible to make small antibiotic packages or uni-doses commercially available. As this problem is not confined to Belgium and the actors involved (i.e. the pharma) are operating in an international context, collaboration with other European countries will be indicated.

11.21 Define new goals regarding antibiotics in the veterinary sector

Since 2006, European legislation banned the use of antibiotics as growth promoters.⁴⁹⁶ Over the years, it resulted in a decreased use of feed medicated with antibiotics. The 2018 BelVet-SAC report (with 2017 data) demonstrated a cumulative reduction of the use of antibiotic premixes of 66.6% and of the use of the 'red' group of antimicrobials (i.e. 3rd and 4th generation cephalosporins and fluoroquinolones, see also section 6.2.2.2) with 84.4% since the reference year 2011. In other words, for both indicators the AMCRA objective (i.e. a 50% reduction in the use of antibiotic premixes by 2017 and a 75% reduction of the use of the 'red' group of antimicrobials by 2020), ratified by the Belgian government in 2016 has already been achieved.¹³¹

In order to avoid a standstill, the One Health AMR action plan should include new goals, which should be defined together with the stakeholders.



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■ APPENDICES

APPENDIX 1. DETERMINANTS OF ANTIBIOTIC PRESCRIPTION AND USE IN HUMANS

Appendix 1.1. Summary of methods for literature search

Search strategy

For studies involving Belgium: Pubmed search in the period January 2000 and 30 April 2018. Search terms: (("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotic"[All Fields]) AND ("prescriptions"[MeSH Terms] OR "prescriptions"[All Fields] OR "prescription"[All Fields]) AND ("belgium"[MeSH Terms] OR "belgium"[All Fields])) AND ("2000/01/01"[PDAT] : "2018/04/30"[PDAT]). 124 titles were found. Other relevant peer-reviewed primary studies found in the references of included articles or transmitted by Belgian experts and/or reviewers were also included. Studies from the grey literature (reports, abstracts and presentations) were found by google search and transmitted by experts, stakeholders and reviewers.

Selection criteria: studies conducted in Belgium or including Belgian subjects; studies looking at the association between (any) antibiotic use and determinants at individual or societal/country level – except clinical factors. Were excluded: studies looking at the choice of specific antibiotics; studies looking at the association between antibiotic use and specific interventions (these are included in chapter 6); studies looking at the association between antibiotic use and specific clinical criteria. Overall, 30 articles were retrieved, including 20 articles on the determinants of antibiotic prescription (Table 53), and 10 articles on the determinants of antibiotic compliance and self-medication (Table 55).

For studies from other settings, we focused on systematic reviews. The systematic review from Public Health England (PHE), with search date up to June 2013, was first retrieved.¹⁸⁹ We searched for more recent systematic reviews in the period 1 January 2013 to 30 April 2018, based on PHE search, using Pubmed search. The search terms were: (("anti-bacterial



agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotic"[All Fields] AND ("behaviour"[All Fields] OR "behavior"[MeSH Terms] OR "behavior"[All Fields])) AND (Review[ptyp] AND ("2013/01/01"[PDAT] : 2018/04/30"[PDAT])). 491 titles were found.

Were only included studies from countries with similar settings, i.e. Western Europe and North America. The inclusion criteria are the same as described for Belgian studies. In addition, determinants that were related to specific characteristics of a country health system were not included (e.g. specific practice organisation, training, phone based consultations). Overall, five relevant systematic reviews were retrieved (Table 54).

Because very few studies on the adherence to antibiotic treatment were retrieved by the above searches, we also conducted a separate Pubmed search focused on Belgium with the search terms: (("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotic"[All Fields]) AND adherence[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND ("belgium"[MeSH Terms] OR "belgium"[All Fields])) AND ("2000/01/01"[PDAT] : "2018/04/30"[PDAT])). The same selection criteria as above were used, and we also excluded studies on the adherence to long-term antibiotic treatment (such as for tuberculosis or cystic fibrosis). In addition, we included multi-country studies including European countries, found in reference of selected studies.

We also conducted a separate search on self-medication or auto-medication by using the search terms ("Self Medication"[Majr:noexp] AND "Anti-Bacterial Agents"[Mesh]) AND ("europe"[MeSH Terms] OR "europe"[All Fields]) AND ("2000/01/01"[PDAT] : "2018/04/30"[PDAT])). Only quantitative studies involving Belgian subjects were retrieved (Table 55).



Appendix 1.2. Characteristics of included Belgian studies and reviews

Table 53 – Characteristics of studies describing determinants for antibiotic prescription in Belgium

Source	Method	Period covered	Study population
Coenen et al., 2000 ¹⁶⁶	Focus group interviews on coughing (fictive case), qualitative	1998	24 Flemish GP
Coenen et al., 2006 ¹⁶²	Interviews on AB prescribing (analysis of cluster RCT), quantitative	2000-01	72 Flemish GP about 1 448 adult patients with acute cough
Coenen et al., 2013 ¹⁷⁰	Prospective observational EU multi-country study, including Belgium, GP and patient interviews, quantitative*	2006-07	2 690 patients with acute cough presenting at 368 GP, including 164 patients and 26 GP from Antwerp
Van Driel et al., 2006 ¹⁷⁵	Observational post-visit survey using questionnaire for GP and patients visiting for acute sore throat, qualitative	2002	68 GP from LOK in 2 provinces and 298 patients
De Sutter et al., 2001 ¹⁶⁸	Information on practice and GP trainer characteristics, quantitative	1996	80 GP trainers of Ghent GP trainees, 722 cases with nose of sinus acute infection
Feron et al., 2007 ^{163, 167}	Focus group discussion, qualitative	Unknown	60 French speaking GP
Tulkens et al., 2016 ¹⁶⁴ (method in Feron) ¹⁸⁰	Lot Quality Assurance Sampling, data on 5 patients, qualitative	Unknown	30 French speaking GP, 150 patients
Feron et al., 2009 ¹⁷¹	Self-administered questionnaire sent to GPs about practice, quantitative	Unknown	221 GP (from 400 randomly selected in 30 French speaking Belgium)
Deschepper et al., 2002 ¹⁶⁹	Interviews persons on self-reporting AB use for URTI episodes, qualitative	1997-98	69 persons from BE and NL cities.
Deschepper et al., 2008 ¹⁷⁷	Comparison of country antibiotic use in databases to cultural scores in EU, quantitative	1997-2003	27 countries including BE
Tyrstrup et al., 2017 ³⁵	Comparison of antibiotic prescription and consultation rates (BE: Intego), quantitative	2012	All consultations for acute infections in 3 countries. In BE: data from 94 GPs Flanders
Van Eldere et al., 2007 ¹⁷²	Database analysis of prescriptions (IMS data) and patient residence, quantitative	1995-2004	All ambulatory patients in 147 districts and their prescribers
INAMI/RIZIV report ¹⁶⁵	Database analysis of prescriptions (Pharmanet) and prescriber profile, quantitative	2013	All active GP from Belgium (GP with ≥200 patients in the year and AB prescription to ≥10 patients)
Willaert et al., 2018 ¹⁶¹	Database analysis of prescriptions (Pharmanet), quantitative	2008-16	Patients affiliated to SSF and their prescribers
Meus et al., 2018 ¹⁷³	Interview through questionnaire on antibiotic use, quantitative	2018	3 403 members of SSF, not representative (more women and >55 years of age)
Blommaerts et al., 2014 ²¹²	Analysis of data from ESAC (antibiotic use) from other international databases on determinants at country level	1999-2007	32 EU countries including BE



Source	Method	Period covered	Study population
Borg, 2014 ¹⁵⁹	Analysis PPS 2011-12 and Hofstede national scores in 28 EU countries	2011-12	Hospital prescribers of perioperative surgical prophylaxis in EU countries
Borg, 2012 ¹⁵⁸	Analysis Eurobarometer survey and Hofstede national scores in EU	2009	General population interviewed in surveys
Van Duijn et al., 2003 ¹⁷⁶	Interview patients GP practices about RTI, 3 countries, quantitative	Unknown	146 patients (Antwerp) and patients in NL and UK
Van Duijn et al., 2005 ¹⁸⁵	Comparison of GP and antibiotic indicators in three EU countries	2001	Entire population of Belgium, UK and the Netherlands (aggregate country measures)

*: part of the GRACE study; PAP>24: perioperative surgical prophylaxis administered for >24h; IMA: inter-mutualistic agency; PPS: point prevalence survey; RTI: respiratory tract infections; SSF: Socialist Sickness Fund; URTI: upper respiratory tract infection; ESAC: European Surveillance of Antimicrobial Consumption; AB: antibiotic(s)

Table 54 – Characteristics of literature reviews describing determinants for antibiotic prescription

Source	Scope	Type of study included	Search period	Number of studies
Touboul-Lundgren et al., 2015 ¹⁵⁷	Cultural determinants of antibiotic use in primary care in Europe	Qualitative & quantitative, cultural determinants, primary care, ≥2 countries involved, English or French	1997-2015	13 studies, all from Europe
Md Rezal et al., 2015 ¹⁸⁸	Physician knowledge, perceptions, attitude, behaviour towards antibiotic prescribing	Qualitative & quantitative, all levels of care, prescriber, any setting, English	1990-2014	19 studies, 10 in similar settings
Public Health England, 2015 ¹⁸⁹	Prescribing behaviours and contexts contributing to antibiotic resistance	Qualitative & quantitative, behaviour, no low-income setting, English	1946-2013	Unclear. 197 studies but not all are described
Teixeira Rodrigues et al., 2013 ¹⁸⁷	Physician antibiotic prescribing behaviour	Qualitative only, prescribers, any setting, English, Portuguese or Spanish	1987-2011	35 studies, 29 in similar settings
Lopez-Vazquez et al., 2012 ¹⁵⁶	Determinant of antibiotics misprescription in primary care	Quantitative only, ambulatory care, any setting, prescriber and patient, English or Spanish	1987-2008	46 studies, 38 in similar settings

Table 55 – Characteristics of studies describing determinants for antibiotic compliance and self-medication

Source	Method	Period covered	Study population
Francis et al., 2012 ²²¹	Prospective cohort study in 14 EU PHC networks (GRACE, study 1)	2006-07*	2 690 adult patients with acute cough (LRTI) from 13 countries, including 164 from Belgium
Gillespie et al., 2017 ²²²	Analysis of adherence data from three GRACE studies (two cohorts and a trial)	2006-10	1 346 adult patients prescribed amoxicillin from 15 EU countries, including Belgium. Adherence self-reported.
Pechere et al., 2001 ²²⁵	Phone interview on antibiotic experience in last 12 months, beliefs and perception	Not reported	600 randomly selected subjects from each of the 9 countries, including Belgium.
Pechere et al., 2007 ²²⁶		2005	



Kardas et al., 2007²³⁰	Phone interview in 11 countries on antibiotic experience in last 12 months, attitudes to doctors, and leftover drugs		4 514 randomly selected subjects from 11 countries, not including Belgium
Grigoryan et al., 2006²³³	Cross-sectional survey in a city and a rural area for each of 19 EU countries, random sampling per country, mailed questionnaire on antibiotic use in last 12 months	2003	15 548 respondents from 19 countries (including 1 734 from Belgium)
Grigoryan et al., 2007²¹⁷			206 respondents from 19 countries (including Belgium) who used both prescribed antibiotics and self-medication
Grigoryan et al., 2008²³⁴ Grigoryan et al., 2007²¹⁷	Survey using F2F interviews in 12 EU countries, subset of subjects from above, on attitudes and knowledge on self-medication	2003-04	1090 respondents and 251 using self-medication from 12 EU countries (including 99 subjects interviewed and 18 reporting self-medication in Belgium)
Deschepper et al., 2008¹⁷⁷	Comparison of country antibiotic use in databases to cultural scores in EU, quantitative	1997-2003	27 countries including BE



APPENDIX 2. DETERMINANTS OF ANTIBIOTIC PRESCRIPTION AND CHOICE IN VETERINARY MEDICINE

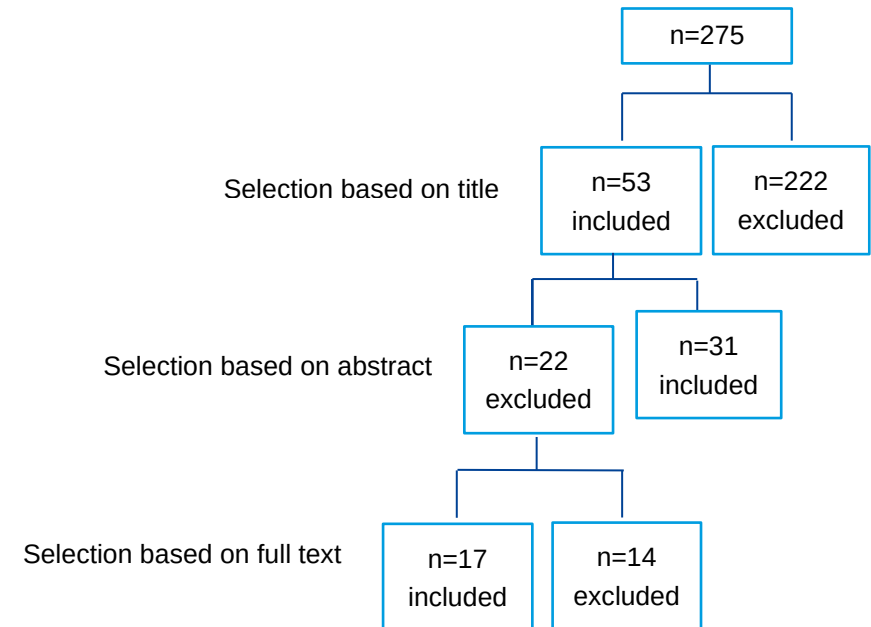
Appendix 2.1. Search strategy

Search in Medline

- 1 Anti-Bacterial Agents/ (305525)
- 2 Anti-Infective Agents/ (49694)
- 3 antibacterial.ab,ti,kw. (60392)
- 4 antibiotic?.ab,ti,kw. (302929)
- 5 anti-bacterial.ab,ti,kw. (2633)
- 6 1 or 2 or 3 or 4 or 5 (533364)
- 7 cattle/ (344907)
- 8 goats/ (30253)
- 9 sheep/ (115973)
- 10 poultry/ (14044)
- 11 sus scrofa/ (11992)
- 12 Livestock/ (2440)
- 13 exp Cattle Diseases/ (69269)
- 14 exp Poultry Diseases/ (22848)
- 15 exp swine diseases/ (29637)
- 16 dairying/ (10843)
- 17 agriculture/ (37690)
- 18 exp Animal Husbandry/ (19398)
- 19 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (579253)
- 20 cows.ab,ti,kw. (44010)
- 21 sheeps.ab,ti,kw. (796)
- 22 goats.ab,ti,kw. (18317)
- 23 cattle.ab,ti,kw. (76182)
- 24 poultry.ab,ti,kw. (23475)
- 25 livestock.ab,ti,kw. (19220)
- 26 ducks.ab,ti,kw. (5354)
- 27 chickens.ab,ti,kw. (33036)
- 28 dairying.ab,ti,kw. (240)
- 29 agriculture.ab,ti,kw. (25567)
- 30 farming.ab,ti,kw. (11469)
- 31 farmer?.ab,ti,kw. (17466)
- 32 pigs.ab,ti,kw. (112927)
- 33 hogs.ab,ti,kw. (654)
- 34 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (343005)
- 35 veterinarians/ (3998)
- 36 veterinary medicine/ (23040)
- 37 veterinar*.ab,ti,kw. (44171)
- 38 35 or 36 or 37 (57704)
- 39 19 or 34 or 38 (804027)
- 40 6 and 39 (23583)
- 41 behavio?r.ab,ti,kw. (748195)
- 42 driver?.ab,ti,kw. (48135)
- 43 factor?.ab,ti,kw. (2965580)
- 44 decision?.ab,ti,kw. (312753)
- 45 determin*.ab,ti,kw. (3242104)
- 46 influe*.ab,ti,kw. (1452526)
- 47 affecting.ab,ti,kw. (245059)
- 48 decision making/ (86408)
- 49 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 (7334715)
- 50 40 and 49 (8636)
- 51 (prescrib* adj3 (factor? or determin* or influe* or driver? or affecting or behavio?r?)).ab,ti,kw. (3481)
- 52 40 and 51 (18)
- 53 ("28625995" or "27748166" or "27516473" or "28026910" or "27371994" or "26890125" or "27317325" or "27443210" or "27142975" or "26934098" or "26891574" or "26891573" or "25960107" or "25903492" or "25785688").ui. (15)
- 54 limit 50 to systematic reviews (50)
- 55 limit 40 to systematic reviews (153)
- 56 limit 55 to yr="2007-2017" (119)
- 57 dogs/ or cats/ (449309)
- 58 animals, domestic/ or pets/ (17124)
- 59 57 or 58 (462546)
- 60 (cats or dogs or 'domestic animals').ab,ti,kw. or animals.ti. (261006)
- 61 59 or 60 (520952)



62 6 and 61 (8576)
63 limit 62 to systematic reviews (72)
64 limit 63 to yr="2007-2017" (48)
65 56 or 64 (147)
66 40 or 62 (30253)
67 49 and 62 (2245)
68 limit 50 to yr="2007-2017" (5135)
69 limit 67 to yr="2007-2017" (1065)
70 exp Prescriptions/ (32217)
71 Practice Patterns, Physicians'/ or Drug Utilization/ (71102)
72 prescription?.ab,ti,kw. (82418)
73 prescrib*.ab,ti,kw. (126492)
74 70 or 71 or 72 or 73 (247366)
75 remove duplicates from 65 (132)
76 40 and 74 (539)
77 62 and 74 (213)
78 76 or 77 (637)
79 remove duplicates from 78 (600)
80 limit 79 to yr="2007-2017" (386)
81 49 and 79 (207)
82 limit 81 to yr="2007-2017" (144)
83 remove duplicates from 82 (144)

Figure 41 – Selection of references



APPENDIX 3. LITERATURE REVIEW OF INTERVENTIONS THAT HAVE BEEN IMPLEMENTED ELSEWHERE

Appendix 3.1. Search strategy of interventions that have been implemented elsewhere

We first looked for useful references included in the Public Health England review.¹⁸⁹ Then we searched for relevant systematic literature reviews included in the reference of the Saha et al.'s systematic review protocol.⁴⁹⁷ We also looked for additional systematic reviews in the Cochrane library using the following search strategy:

Date Run:	25/06/18		
Description:			
ID	Search Hits		
#1	'intervention':ti,ab,kw or 'training':ti,ab,kw or 'campaign':ti,ab,kw or 'program':ti,ab,kw (Word variations have been searched)	257705	
#2	'stewardship':ti,ab,kw or 'prudent use':ti,ab,kw or 'good use':ti,ab,kw or 'overuse':ti,ab,kw or 'good practice' (Word variations have been searched)	3192	
#3	'antibiotic':ti,ab,kw or 'antimicrobial':ti,ab,kw or 'anti-bacterial':ti,ab,kw or 'anti-mycobacterial':ti,ab,kw or 'bacteriocidal':ti,ab,kw (Word variations have been searched)	31509	
#4	#1 and #2 and #3 Publication Year from 2000 to 2018	27	

Finally we looked for randomised clinical trials (RCT) or observational studies aiming to promote prudent use of antibiotic using the following search strategy in the PubMed library:

Date Run:	17/07/18
((((Intervention[Title/Abstract] OR Training[Title/Abstract]) OR Campaign[Title/Abstract]) OR Program[Title/Abstract]) AND (((Stewardship[Title/Abstract] OR Prudent use[Title/Abstract]) OR Good use[Title/Abstract]) OR Overuse[Title/Abstract]) OR Good practice[Title/Abstract])) AND (((Antibiotic[Title/Abstract] OR Antimicrobial[Title/Abstract]) OR Anti-bacterial[Title/Abstract]) OR Anti-mycobacterial[Title/Abstract]) OR Bacteriocidal[Title/Abstract])) AND ('2000/01/01'[PDAT] : '3000'[PDAT]) AND ((Observational Study[ptyp] OR Clinical Trial[ptyp] OR Controlled Clinical Trial[ptyp]) AND 'humans'[MeSH Terms]) AND ((Randomized Controlled Trial[ptyp] OR Observational Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp] OR Clinical Trial[ptyp]) AND 'humans'[MeSH Terms]) 81	

We retained RCTs and observational studies published in English, French or Dutch from January 2000 to July 2018 and performed in EU/EEA country. Additional information on the 65 references whom the whole text was considered in this report are included in Appendix 3.2.

Forty-two (42) references were finally retained for the report. ^{272, 323, 343, 345-383}



Appendix 3.2. References considered for the chapter on interventions that have been implemented elsewhere

Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
Stewardship at hospital level							
Nasal decontamination	1937-2015	<ul style="list-style-type: none">Nasal decontamination for the prevention of surgical site infection in <i>Staphylococcus aureus</i> carriers	<ul style="list-style-type: none">Systematic Protocol Review	NA	NA	498	This is the protocol of a systematic review + nasal decontamination is done with nasal drops (out of the scope of the report) Not included in the report
Multifaceted interventions Persuasive intervention: <ul style="list-style-type: none">Audit and feedbackEducation through meeting and educational materialEducational outreach (academic detailing, review of individual patients and recommendation to change)	1946-2015	<ul style="list-style-type: none">Health care professionals who prescribe antibiotic to hospital in-patients221 studies includedMost included studies were from North America (n=96) and Europe (n=87)	<ul style="list-style-type: none">Systematic review + meta-analysis + meta-regressionRCTs and non RCTsOutput:<ul style="list-style-type: none">Compliance with AB guidelines/policiesDuration of AB therapyDecision to treatTotal duration of the treatmentLength of stayOutcome:<ul style="list-style-type: none">MortalityMicrobial/clinical outcomesUnintended-consequences measures	<ul style="list-style-type: none">There were high levels of heterogeneity of effect size but the direction consistently favoured interventionInterventions were associated with an increase in compliance (= risk difference of prescription) with desired practice by 15 % (95% CI 14-16%)Duration of AB treatment decreased by - 1.95 days (95% CI 1.67-2.22)Interventions are associated with improvement in prescribing according to AB policy in routine clinical practiceRisk of death was similar between intervention and control groups (11% in both arms)	NA	345	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
<ul style="list-style-type: none"> Reminders (paper, verbally, workplace) <i>Structural (paper to computerised prescription; new technology for rapid microbio testing,...)</i> <i>Restriction intervention:</i> <ul style="list-style-type: none"> Selective reporting of laboratory susceptibilities Formulary restriction Requiring prior authorisation Therapeutic substitution Automatic stop orders 				<ul style="list-style-type: none"> AB stewardship interventions reduce length of stay by 1.12 days (95% CI 0.7-1.54 days) 			
<u>Multifaceted interventions:</u> <ul style="list-style-type: none"> Audit and feedback Educational outreach visits Patient-mediated 	1951-2008	<ul style="list-style-type: none"> 29 studies included in the systematic review 	<ul style="list-style-type: none"> Systematic Review CBA, RCT and non randomised controlled trials Output: effectiveness of interventions aiming to improve prescribing 	<ul style="list-style-type: none"> Audit and feedback and educational outreach were the most effective in improving prescribing practices Far less positive for patient-mediated strategies Not enough evidence to draw conclusion about efficacy of manual reminders, consensus processes, multidisciplinary teams 	NA	346	Do not focus on AB Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
<ul style="list-style-type: none"> Reminders-manual Local consensus process Multidisciplinary teams Distribution of educational materials 							
<u>Procalcitonin</u>	1966-2011	<ul style="list-style-type: none"> Hospital level Acute RTIs 14 studies included 4551 patients 	<ul style="list-style-type: none"> Systematic Review Procalcitonin to initiate or discontinue antibiotics in RTIs Only RCT included Output: antibiotic use, length of hospital stay for hospitalised patients, length of ICU stay for critically ill patients, number of days with restricted activities within 14 days Outcomes: All-cause of mortality following randomisation up to a follow-up time of 30 days, treatment failure (death, RTI complication) 	<ul style="list-style-type: none"> No difference in all-cause mortality in procalcitonin group patients compared to control patients (5.7% vs. 6.3%, OR 0.94, 95% CI 0.71-1.23). This was consistent across clinical settings and RTI diagnoses Overall, a significant lower risk for treatment failure in procalcitonin-treated patients compared to control patients (19.1% vs. 21.9%, OR 0.83, 95% CI 0.71-0.97) Total antibiotic exposure was significantly reduced overall, from 8 (IQR 5-12) to 4 (IQR 0-8) days 	NA	³⁴⁷	<p>Interesting and useful study for the report</p> <p>Included in the report</p>
<u>Guidelines</u> <u>De-escalation of therapy based on culture (change</u>	1979 - 2014	<ul style="list-style-type: none"> 145 studies included in the systematic review 	<ul style="list-style-type: none"> Systematic Review and meta-analysis RCTs and non RCTs included Output: 	<u>Guidelines</u> <ul style="list-style-type: none"> Of the 37 studies reporting data on empirical treatment according to guidelines, 31 showed that prescribing according to guidelines 	Yes, see results primary outcome column	²⁷²	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Refere nce	Remark and Critical appraisal of review quality
<p>to narrow-spectrum AB or stop AB as soon as culture results are available)</p> <p><u>Adjusting therapy according to renal function</u></p> <p><u>Switch IV to oral AB</u></p> <p><u>Therapeutic drug monitoring</u></p> <p><u>Discontinuation of empirical treatment based on no evidence of infection</u></p> <p><u>Presence of a local AB guide</u></p> <p><u>Restricted list of AB</u></p> <p><u>Bedside consultation the overall evidence</u></p>			<ul style="list-style-type: none"> - Costs - Length of stay (LOS) • Outcome <ul style="list-style-type: none"> • Mortality rate 	<p>was associated with reduced morality, with 14 studies showing significant associations. The RRR for mortality across all studies was 35 % (RR 0.65, 95% CI 0.54-0.80, $p < 0.001$)</p> <ul style="list-style-type: none"> • 17 studies showed decreased durations of hospital LOS (significant in 8) • 4 studies reporting data on costs indicated that savings were made with adherence to guidelines (significant in 2 studies) <p><u>De-escalation of therapy based on culture</u></p> <ul style="list-style-type: none"> • 17 studies showed decreasing of morality rate (7 being significant). RRR for mortality across studies was 56% (RR 0.44, 95% CI 0.30-0.66, $p < 0.0001$) • 9 studies suggested decreased duration (only two showed significant effects). The tenth (a RCT) showed non-significant increase of LOS • 11 studies showed savings when comparing de-escalation of therapy with unmodified therapy (five reported significant differences) <p><u>Adjusting therapy according to renal function</u></p> <ul style="list-style-type: none"> • One study noted a non-significant positive effect on mortality and a significant shortening of ICU LOS – other studies had poor quality <p><u>Switch IV to oral AB</u></p>			



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
				<ul style="list-style-type: none"> • Four studies showed a non-significant beneficial effect on mortality rate – one showed a non-significant negative effect – The overall effect on mortality rate was non-significant. • 11 studies reported data one cure or resolution, none showed significant effect • 2 observational studies and 5 RCTs showed significant effects on reducing LOS • Costs were reduced in 3 observational studies and 8 RCTs (2 and one had significant results) <p><u>Therapeutic drug monitoring</u></p> <ul style="list-style-type: none"> • None of the 16 studies showed significant effect on mortality rate – the overall effect on mortality was non-significant • Four of five RCTs and non-RCTs reported shorter LOS in hospital in whom drugs were monitored than those in whom there were not – In four of the 6 observational studies, LOS was shortened as well • 13 studies reported on the rate of nephrotoxicity. RRR was significant at 50% (RR 0.50, 95% CI 0.29–0.88, p=0.02) • Wide variation on costs data but overall there seemed to be a beneficial effect (cost savings) <p><u>Discontinuation of empirical treatment based on no evidence of infection</u></p>			



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Refere nce	Remark and Critical appraisal of review quality
				<ul style="list-style-type: none"> Only 3 studies reported on discontinuation of therapy due to clinical or microbiological evidence of infection and the overall quality of evidence was low (non-significant impact on mortality rate, one RCT showed a significant decreasing in ICU LOS, one RCT reported reducing in costs) <p><u>Presence of a local AB guide</u></p> <ul style="list-style-type: none"> Only one observational study evaluated that intervention. It showed a decreasing of mortality rate in patients with community-acquired infections, nosocomial infections and postoperative intra-abdominal infections (low quality of evidence) <p><u>List of restricted AB</u></p> <ul style="list-style-type: none"> The overall effect on mortality was limited and non-significant LOS reduced significantly in 2 observational studies Nosocomial infection rates were reported in 5 observational studies, with one showing a significant decrease and one a significant increase All (except one) showed reduced costs (significant effects seen in four) Resistance rates were assessed in 26 studies. Overall restrictive measures were effective, with the amount of monthly prescribed DDD of restricted AB being significantly lower than without restriction. Resistance rates for restricted AB were significantly decreased across a 			



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Refere nce	Remark and Critical appraisal of review quality
				<p>wide variety of infective agent and drug combinations. A few studies reported increased resistance rates for non-restricted AB</p> <p><u>Bedside consultation</u></p> <ul style="list-style-type: none"> • Despite five observational studies showed decreased mortality with bedside consultation (significant effects seen in 3), overall effect on mortality was not significant – high heterogeneity • Three studies reported the effect on hospital LOS. One showed a decrease, two showed an increase (one being significant) • Only two studies reported on costs and results were contradictory <p>! Quality of the evidence is generally low!</p>			
<u>AB committee</u> <u>Written AB policy</u> <u>Written AB formulary</u> <u>Restricted AB list</u> <u>Drugs and therapeutic committee</u> <u>Strategic management goal of improving prescribing</u>	January 2002 – June 2005	<ul style="list-style-type: none"> • EU-30 countries • 170 hospitals participated 	<ul style="list-style-type: none"> • Observational study • Utilisation of a questionnaire to request data on AB prescribing • Aim is to evaluate presence/absence of AB policy in hospital 	<ul style="list-style-type: none"> • No evaluation of the interventions • Policies and practices relating AB stewardship varied considerably across European hospitals 	NA	499	<p>None evaluation of the interventions</p> <p>Not included in the report</p>



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
<u>Procalcitonin</u>	December 2002-April 2003	<ul style="list-style-type: none"> Switzerland (Basel) One university hospital (784 beds) – Emergency department 243 patients Lower RTI 	<ul style="list-style-type: none"> cRCT Intervention: PCT vs standard care A PCT value of 0.1–0.25 µg/L was regarded as an indication that bacterial infection was unlikely, and they discouraged use of antibiotics Outcome: use of AB 	<ul style="list-style-type: none"> Proportion of AB prescribed was significantly lower in the PCT group than in the standard group (44% vs. 83%, $p<0.0001$) Duration of treatment was significantly lower in PCT group than in standard group (10.9 vs. 12.8, $p<0.0001$) AB costs per patient was significantly lower for the PCT group (96.3\$ vs. 202.5\$, $p<0.001$) Clinical outcomes were similar in both groups 	NA	366	Included in the report
<u>Electronic decision support tool</u>	2004-2006	<ul style="list-style-type: none"> USA (Baltimore) Children's hospital (176-bed) 	<ul style="list-style-type: none"> Web-based programme includes: an automatically generated inpatient census, lists of restricted and unrestricted antimicrobials, a notification system with text paging and e-mail reminders about requests (approved, disapproved, ...), and an 'automatic' approvals for specific drug indication combinations Output: satisfaction of prescribers and pharmacists, delivery times for restricted and unrestricted antimicrobials, evaluation of the number of dispensed restricted and unrestricted antimicrobial doses, and evaluation of the cost of dispensed 	<ul style="list-style-type: none"> After implementation, there was 11.6% reduction in the number of dispensed doses User satisfaction increased from 22 to 68% and from 13 to 69% among prescribers and pharmacists, respectively 	<ul style="list-style-type: none"> The annual cost of restricted AB decreased from the projected costs by \$370 069 within a year after implementation of the online ASP. Cost of unrestricted AB was similar (~\$570 000) during both periods 	500	USA, not RCT Not included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
			restricted and unrestricted antimicrobials				
<u>Multifaceted interventions:</u> <ul style="list-style-type: none"> AB committee Prescription support with stop-orders IT support for prescribing or for pharmaceutical analysis Educational activities Practice audits 	2005-2009	<ul style="list-style-type: none"> France (south-western) Hospital (n=74) 	<ul style="list-style-type: none"> Longitudinal study (but data retrospectively collected) Estimate the impact of ASP measures and trends in antibiotic use Output : daily doses/1000 patient-days 	<p><u>Overall</u></p> <ul style="list-style-type: none"> Globally AB use (DDD/1000 patient days) remained stable over the years: +2.5%. None of the variation by AB type was significant <p><u>Audit</u></p> <ul style="list-style-type: none"> Audits on prescribing practices seem to predict decrease in total AB use (OR 6.1, 95% CI 1.2-32.4) <p><u>AB advisor</u></p> <ul style="list-style-type: none"> Time devoted by the AB advisor seems to predict decrease in fluoroquinolone use (OR 5.7, 95% CI 1.4-22.9) 	NA	379	<p>Practice audit and AB advisor seem to have significant impact on AB use</p> <p>Included in the report</p>
<u>Computer-assisted decision support</u>	<ul style="list-style-type: none"> January-April 2006 February-April 2007 August to October 2009 February to March 2010 	<ul style="list-style-type: none"> France One university hospital (five intensive care units) 1 316 patients included in the analysis 	<ul style="list-style-type: none"> Prospective before/after cohort study Intervention period followed by three post-interventions periods (p1, p2 and p3) Intervention Computer-assisted decision support was designed to provide clinicians with essential guideline-based information concerning the treatment of infections, the use of antibiotic agents and 	<ul style="list-style-type: none"> A net increase of 10% guideline adherence was observed during the 5-year observation period Antibiotic-free days increased over time starting from 30% of all ICU days and finally achieving 42% (p3) (p<0.01) Mortality rate was significantly lower for patients with guideline adherence of the physicians > 70% (12.3%) than adherence <70% (8%, p=0.014) 	NA	375	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
			microbial diagnostics in the intensive care units <ul style="list-style-type: none"> • Output: adherence to guideline, antibiotic-free days • Outcome: mortality rate 				
<u>Procalcitonin</u>	February 2006 to April 2007	<ul style="list-style-type: none"> • Switzerland • One tertiary care hospital (1 200 beds) • 68 patients • Sepsis 	<ul style="list-style-type: none"> • RCT • Intervention was PCT use a point-of-care. The algorithm used was: investigators encouraged treating physicians to discontinue AB when 1) PCT dropped more than 90% from the baseline peak level, 2) or an absolute value below 0.25 µg/L was reached • Output: duration of AB treatment, incidence density of AB exposure days, day alive without AB 	<ul style="list-style-type: none"> • In patients in whom a decision could be taken based on serial PCT measurements, PCT guidance resulted in a 4-day reduction in the duration of antibiotic therapy (per protocol, n=68, p=0.003) and a smaller overall antibiotic exposure (p=0.0002) • A similar mortality and recurrence of the primary infection were observed in PCT and control groups. A 2-day shorter intensive care unit stay was also observed in patients assigned to the PCT group (p=0.03) 	NA	³⁶¹	Included in the report
<u>Guidelines on IV-oral AB switch</u>	December 2006-June 2007	<ul style="list-style-type: none"> • Ireland • 753 beds university hospital • Adults patients admitted via the emergency department 	<ul style="list-style-type: none"> • Prospective controlled before-after • Intervention: <ul style="list-style-type: none"> - Application of stickers to the drug chart by clinical pharmacists, highlighting that the patient was on IV AB - Application of guidelines to the drug chart by clinical pharmacists, with 	<ul style="list-style-type: none"> • The duration of IV antimicrobial treatment reduced significantly in the study group postintervention, compared to the control group (72 vs 96 hours, p=0.02) • The timeliness of the switch also improved significantly in the study group post-intervention (71.7% vs. 55.5%, p=0.017) • No improvement occurred in the control group 	If extrapolated to 1 year, the saving in initial intravenous antimicrobial therapy would be €16 203, or a net saving of 5.9%, if the intervention were to be	⁵⁰¹	This is focus on guidelines and therefore out of the scope of the report Not included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
			<ul style="list-style-type: none"> criteria for an IV to PO antimicrobial switch. - Junior doctors working for hospital physicians were contacted when necessary by clinical pharmacists to request consideration of an IV to PO switch, once the patient had met criteria for switch. • Output: duration of the IV AB therapy 	<ul style="list-style-type: none"> The median length of stay was not reduced post-intervention. 	implemented to medical patients admitted throughout the hospital		
<u>AB Multidisciplinary team</u>	2009-2014	<ul style="list-style-type: none"> • France • One university hospital (Nancy) on 2 sites (site 1: 484 beds, no team vs. site 2: 720 beds, team) 	<ul style="list-style-type: none"> • Cluster-controlled trial • This study aimed to evaluate the medium to long-term effect (2 to 7 years) of an implemented AB multidisciplinary team • Team was made up of a pharmacist and a physician specialised in infectious diseases • The intervention was previously implemented in 2007 by Bevilacqua et al.⁵⁰² • Output: use of AB and cost savings 	<ul style="list-style-type: none"> • Reduction in antibiotic use continued but at a lower rate than in the short term (11% between 2009 and 2014 compared with 33 % between 2007 and 2009) • Principal decreases concerned fluoroquinolones and glycopeptides • Cost fell 10.5% in the intervention group vs 5.7% in the control group between 2009 and 2014 	NA	358	Included in the report
<u>Procalcitonin</u>	<ul style="list-style-type: none"> • September 2009-July 2013 	<ul style="list-style-type: none"> • Netherlands • 3 university medical centres and 12 teaching hospitals 	<ul style="list-style-type: none"> • RCT • Intervention is the implementation of procalcitonin measurements and 	<ul style="list-style-type: none"> • Median use of antibiotics was 7.5 DDD (IQR 4.0-12.7) in the procalcitonin group versus 9.3 DDD (IQR 5.0-16.6) in the standard group 	<ul style="list-style-type: none"> • Total reduction in antibiotic costs using procalcitonin 	359	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
		<ul style="list-style-type: none"> Intensive care unit 1 575 patients 	<p>guidance (advice to stop the prescribed antibiotic if procalcitonin concentration had decreased by 80% of more of its peak value or when it reached a value of 0.5 µg/L or lower) vs standard-of-care groups</p> <ul style="list-style-type: none"> Output: AB DDD and duration of AB treatment Outcome: Mortality rate 	<p>(between-group difference 1.22, 95% CI 0.65-1.78, $p<0.001$)</p> <ul style="list-style-type: none"> Duration of treatment was significantly lower in the procalcitonin group (5 days vs. 7 days, absolute difference 1.22 days, IQR 0.65-1.78, $p<0.001$) Mortality at 28 days was significantly lower in the procalcitonin group (20 vs. 25%, absolute difference 5.4%, 95% CI 1.2-9.5, $p=0.0122$) 	<p>n guidance was a mean of € 34 per patient. In this study a mean of 7 procalcitonin measurements were taken per patient; therefore, the reduction in AB costs will only outweigh the costs of additional procalcitonin measurements if procalcitonin tests costs less than 4 euro per measurement.</p>		
<u>Post-prescription systematic review</u>	May 2010 to April 2011)	<ul style="list-style-type: none"> France Four hospitals in Paris 2 surgical or medical wards per hospital were selected as 	<ul style="list-style-type: none"> Multicenter RCT 'ANTIBIOREF' trial Intervention: Audit, i.e. postprescription systematic review by the ASP infectious disease 	<ul style="list-style-type: none"> Appropriateness of the treatment was more frequent in the intervention group (44.7% vs. 28.5%, $p=0.008$) AB treatment duration was lower in the intervention group (Median 7 days (IQR 3-9) vs. 10 (IQR 7-12); $p=0.003$) 	NA	³⁵⁷	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
		<ul style="list-style-type: none"> having a high level of AB use 246 patients 	<ul style="list-style-type: none"> physicians at day 1, 3 and 4 Output: appropriateness of AB therapy (using composite score), treatment duration 	<ul style="list-style-type: none"> ASP physicians counselling to change therapy was more frequent at day 3 to 4 than at day 1 Clinical outcome was similar in both group 			
<u>Multidisciplinary infectious diseases team</u>	October 2011-May 2012	<ul style="list-style-type: none"> Belgium Tertiary hospital, 1062 beds 	<ul style="list-style-type: none"> Prospective observational study Intervention: initiation of a multidisciplinary infectious diseases team (MIT) as part of an antimicrobial stewardship MTI included infectious disease physicians, clinical microbiologists and clinical pharmacists MTI pharmacists registered every recommendation communicated by the MTI during 87 days Aim of the study was to describe the type and acceptance rate of interventions provided by the MIT A score of acceptance was created 	<ul style="list-style-type: none"> The MIT communicated 432 recommendations in 87 days observed Recommendations were made to perform additional clinical investigation(s) (n=5 137, 27%), to adjust the dose of an antimicrobial drug (n=542, 8%), to stop an antimicrobial drug (n=5104, 21%), to switch from a parenteral to an oral drug (n=539, 8%) or to initiate an antimicrobial drug (n=5 178, 36%), with an acceptance rate of 73.0%, 83.3%, 81.7%, 76.9%, and 84.0%, respectively 	NA	²⁸¹	Not Included in the report (but in the <i>Belgian interventions chapter</i>)
<u>Quality indicators</u>	October 2011-2012	<ul style="list-style-type: none"> Hospital level The Netherlands: 22 hospitals and 1890 inpatients 	<ul style="list-style-type: none"> Cross-sectional point-prevalence multicentre study Measurability, applicability and 	<ul style="list-style-type: none"> Seven QIs demonstrated to have clinimetric properties 	NA	⁵⁰³	This study is the evaluation of the applicability of the checklist used in



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
			reliability for developed QIs				³⁵⁶ is evaluated. Not included in the report
<u>Antibiotic stewardship programmes</u>	2012-2017	<ul style="list-style-type: none"> Hospital level 8 studies included 	<ul style="list-style-type: none"> Systematic review Output: evidence that ASP are effective strategies for preventing AB resistance 	<ul style="list-style-type: none"> There was great heterogeneity regarding the measure used to evaluate the impact of the programmes on resistance. The clear majority (62%) of the studies used the proportion of resistant isolates in relation to the total number of isolates No solid evidence that ASPs are effective in reducing AB resistance in hospital settings 	NA	⁵⁰⁴	Interesting study but there was great heterogeneity in the results and conclusions are not useful for the chapter on international interventions. Not included in the report
<u>Selective reporting of AB susceptibility data</u>	2012	<ul style="list-style-type: none"> France Three French universities (Dijon, Nice, Saint-Etienne) 326 residents training in GP Urinary tract infection (UTI) 	<ul style="list-style-type: none"> Prospective randomised-controlled case-vignette study Intervention was a selective reporting of AB susceptibility data (2 to 4 AB only) 	<ul style="list-style-type: none"> For all UTI scenarios, selective reporting of AB susceptibility data significantly improved the appropriateness of AB prescriptions 	NA	⁵⁰⁵	Not tested in real situation, i.e. only on students at university. Not included in the study
<u>Multiplex PCR</u>	March 2012-November 2013	<ul style="list-style-type: none"> Switzerland One academic hospital (1 900 beds) 89 patients Bacteraemia 	<ul style="list-style-type: none"> RCT Intervention: triplex real-time PCR vs conventional work-up to identify staphylococcal species with methicillin susceptibility Output: time for Gram stain results to targeted 	<ul style="list-style-type: none"> Median time from Gram stain to transmission of methicillin-susceptibility was significantly lower for the intervention group than for the standard group (3.9 hours, IQR 2.8-4.3 vs. 25.4 hours, IQR 24.4-26.7; p<0.001) Median time from Gram stain to targeted treatment was significantly shorter in the intervention group 	NA	³⁶⁴	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
			therapy in both groups, length of hospitalization <ul style="list-style-type: none"> Outcome: presence of septic complications, infection related mortality 	when considering <i>S.aureus</i> only (5 hours, IQR 3-7 vs. 25.5, IQR 3.8-54, $p<0.001$) <ul style="list-style-type: none"> When standard susceptibility testing was complete, 85.4% of the patients in the intervention group were already receiving targeted therapy compared to 56.1% in the control group ($p=0.004$) No difference on clinical outcomes 			
<u>Procalcitonin</u>	October 2012 to July 2013	<ul style="list-style-type: none"> Denmark Copenhagen University Hospital Bispebjerg (monocentric) Patients hospitalized with acute exacerbation of COPD (n=120) 	<ul style="list-style-type: none"> RCT Intervention was PCT use a point-of-care. The algorithm used was: initiation or continuation of AB was strongly discouraged if PCT was 0.15 ng/mL or lower and discouraged if levels were between 0.15 and 0.25 ng/mL. Initiation or continuation of AB was encouraged if PCT was > 0.25 ng/mL. Blood samples for PCT measurement were collected within 24 hours of admission and on days 3, 5 and 7 of admission. Output: Proportion of patients using AB, duration of hospitalisation Outcome: Adverse event, mortality, etc. 	<ul style="list-style-type: none"> Proportion of patients using AB for ≥ 5 days within the 28-day follow-up was lower in the PCT group than the standard group (CRP) (41.9% vs. 67.2%, $p=0.006$) Duration of AB exposure was lower in PCT group than standard group (3.5, IQR 0-10 vs. 8.5, IQR 1-11, $p=0.0169$) No apparent difference was observed in the mortality rate and adverse outcomes 	NA	365	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Refere nce	Remark and Critical appraisal of review quality
<u>Checklist</u>	November 2014- October 2015	<ul style="list-style-type: none"> Hospital level The Netherlands: 8 hospitals – 853 baseline patients and 5 354 interventions patients Intravenous antibiotics 	<ul style="list-style-type: none"> cRCT Quality indicators (QIs) included in a checklist that define appropriate AB use in the treatment of bacterial infections in the hospital QIs were: blood cultures, cultures of suspected site of infection, guideline adherence, documented AB plan, adapt therapy when culture results become available, IV-oral switch. Education, feedback and reminders were also organized for the participating physicians Outcome: length of stay (LOS) Output: appropriate antibiotic treatment according to the generic quality indicators (defined by a score) and total antibiotic use defined by days of therapy (DOT) 	<ul style="list-style-type: none"> LOS did not change after intervention Antibiotics were used more appropriately according to QIs after the introduction of the AB checklist. The percentage of patients with a QI sum score above 50% increased significantly by 18.7 % ($p<0.001$) 	NA	356	Included in the report
<u>Multiplex PCR</u>	January- July 2015	<ul style="list-style-type: none"> UK (London) 900 beds tertiary hospital Upper/lower RTI, influenza-like illness 	<ul style="list-style-type: none"> Quasi-randomised trial Intervention: multiplex PCR versus routine tests Study-ward staff were educated about the study and consent taking, given a staff information 	<ul style="list-style-type: none"> Multiplex intervention was not associated with the length of stay, but reduced the turn-around-time from 39.5 h to 19.0 h, $p<0.001$ Only the prescribing decision differed between study arms, $p<0.001$. When antivirals were given, the intervention was associated with a reduction in 	The FilmArray® is relatively expensive compared to currently employed routine tests	367	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
		<ul style="list-style-type: none"> 545 patients enrolled 	sheet and trained to use the FilmArray® <ul style="list-style-type: none"> Output: length of stay and AB use 	the median time to the first dose of 36 h and allowed appropriate treatment of mycoplasma infection	but savings from the shorter hospital stay may offset the extra test costs and prove cost beneficial		
<u>Selective reporting of AB susceptibility data</u>	October-July 2015	<ul style="list-style-type: none"> France (Lorraine) 131 GPs 	<ul style="list-style-type: none"> Prospective randomised-controlled case-vignette study Intervention was a selective reporting of AB susceptibility data 	<ul style="list-style-type: none"> For 3/4 scenarios, selective reporting of AB susceptibility data significantly improved the appropriateness of AB prescriptions 	NA	506	Not tested on real cases but that time on GPs (instead of students). Not included in the report
<u>Antimicrobial stewardship teams</u> <u>Prevention of surgical infections with <i>S. aureus</i> using screen and treat strategies</u>	2016	<ul style="list-style-type: none"> Netherlands + other EU countries Hospital level 	<ul style="list-style-type: none"> Synthesis and expert opinion of most cost-effective infection prevention and adequate use of AB 	<u>Antimicrobial stewardship teams</u> <ul style="list-style-type: none"> Antimicrobial stewardship teams are mandatory for every Dutch hospitals. A hospital estimated a €40 000 hospital wide cost-saving over a 12-month period after introduction of the antimicrobial stewardship team. https://www.cwz.nl/over-cwz/nieuws-en-pers/nieuwsoverzicht/cwz-a-team-waakt-over-veilig-antibioticagebruik/ Significant reduction of the number of prescriptions, switch earlier to oral therapy, had a shorter length of hospital stay and required less nursing³⁸⁷ <u>Prevention of surgical infections with <i>S. aureus</i> using screen and treat strategies</u>	<u>Antimicrobial stewardship teams</u> <ul style="list-style-type: none"> In the urology department³⁸⁷ and during the programme's first year, the study group spent almost €70 000 less than the historical cohort, while the total cost of the intervention 	354	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
				<ul style="list-style-type: none"> Reduction in use of AB can also be capitalized by a reduction of infections. Removal of <i>S.aureus</i> from the nose before surgery has shown to prevent infections. Screen-and-treat strategies have been proved to be effective^{507, 508} and highly cost-effective⁵⁰⁹ 	were about €27 000 <ul style="list-style-type: none"> Structural costs: €17 000 (meetings and development of the e-alert programme), structural costs totalled about €10 000. Possible return on investment of €700 		
<u>All interventions</u>	Unknown	<ul style="list-style-type: none"> 43 studies included in the systematic review 	<ul style="list-style-type: none"> Systematic review RCT, quasi-RCT, CBA Outcome: Rate of antibiotic use 	<ul style="list-style-type: none"> For delayed prescription, the median rate of antibiotic use was lower in intervention compared to control groups (37.5%) 	NA	⁵¹⁰	Study's quality seems not guaranteed Not included in the report
<u>Interventions involving pharmacists</u>	NA	NA	<ul style="list-style-type: none"> Protocol of a systematic review of interventions involving pharmacists in strategies to improve AB prescriptions by GP 	NA	NA	⁴⁹⁷	Reference list of this protocol was investigated in the search strategy Not included in the report
<u>All interventions</u>	NA	<ul style="list-style-type: none"> Mainly USA Hospital level 	<ul style="list-style-type: none"> Synthesis of existing stewardship 	<ul style="list-style-type: none"> Antimicrobial stewardship strategies highlighted were: 	NA	⁵¹¹	Useful to highlight



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
			programmes in health care systems with advantages and disadvantages	<ul style="list-style-type: none"> • Education /guidelines (Advantages (Adv) = may alter behaviour patterns and avoid loss of prescriber autonomy. Disadvantages (dis) = passive education likely ineffective) • Formulary/restriction (Adv = Most direct control over antimicrobial use, individual education opportunities. Dis = perceived loss of autonomy for prescribers, need for all-hours consultant availability) • Review and feedback (Adv = avoid loss of autonomy for prescribers and individual educational opportunities. Dis = compliance with recommendations voluntary) • Computer assistance (Adv = provides patient-specific data where most likely to impact (point-of-care), facilitates others strategies. Dis: significant time and resource investment to implement sophisticated systems.) • Antimicrobial cycling (Adv = may reduce resistance by changing selective pressure. Div = difficult to ensure adherence to cycling protocol and theoretical concerns about effectiveness) • Future directions of research and practice can be: 			<p>advantages and disadvantages of antimicrobial stewardship strategies but do not propose/evaluate interventions</p> <p>Not included in the report</p>



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
				<ul style="list-style-type: none"> Development and spread of computerized Order-Entry and Decision Support Systems Antimicrobial Use Surveillance and Benchmarking Locally and Nationally 			
<i>Stewardship at ambulatory level</i>							
<u>All interventions</u>	... to 2012	<ul style="list-style-type: none"> Parents & Clinicians 17 studies included Most studies from the USA (n=10); followed by Israel (n=3), Europe (n=3) and Australia (n=1) Respiratory infection in children (<18 years) Primary care (family practice, emergency, paediatric primary care) 	<ul style="list-style-type: none"> Systematic review RCT and Non RCT included Output: Change in proportion of AB prescriptions for RTIs in children OR change in 'appropriate' AB prescribing 	<ul style="list-style-type: none"> 8/10 interventions which targeted both clinicians and parents reported significantly decreased prescribing rates (range 6-21%) Largest effect observed in a study which used a combined parent-clinician 'interactive book' (19.5% reduction prescribing rate)⁵¹² Only one study that targeting clinicians only reported reduction in AB prescribing⁵¹³ but two reported significant reductions in inappropriate prescribing^{514, 515} None of the interventions directed only at parents significantly reduced AB prescribing. Most effective interventions involved targeting both parents and clinicians during a consultation⁵¹², providing automatic computer prompts for evidence-based prescribing⁵¹⁴ and promoting clinician leadership or participation in the design of treatment guidelines and/or peer education^{516, 517, 518} Moderately strong evidence that interventions were more effective in reducing AB prescribing when 	NA	³⁴⁹	<p>Interesting and useful study. More appropriate prescribing for RTIs in children may be achieved when interventions are designed in consultation with participants, incorporate changes into everyday prescribing processes, and address the needs of parents and clinicians.</p> <p>Included in the report</p>



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
				delivered to clinicians in collaboration with parents			
<u>All interventions</u>	... to 2012	<ul style="list-style-type: none"> • 4 RCTs were included (2 in Canada, 1 Sweden, 1 in USA) • In Long-term care facilities (LTCF) 	<ul style="list-style-type: none"> • Aim of the review was to collect and interpret results of studies of interventions to improve the quality of, or appropriateness of antibiotic prescribing in LTCF • Systematic review • Only RCT included 	<ul style="list-style-type: none"> • Three studies directed educational material and sessions at physicians and nurses, with one of the three studies providing prescribing feedback as well. The fourth study provided educational material and prescribing feedback for physicians only • Due to the mixed and modest effects of the intervention, none intervention was evaluated as being successful. • They still concluded that multifaceted intervention involving small group educational sessions and the provision of educational material was generally acceptable to nurses and physicians in LTCF • Involvement of local consensus procedures when developing guidelines and interventions may improve the success of intervention • Quality of evidence is low 	NA	³⁵²	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
<u>All interventions</u>	1966-2002	<ul style="list-style-type: none"> Ambulatory care 39 studies included 	<ul style="list-style-type: none"> Systematic review that included RCT, QRCT, ITS Output: synthesized existing interventions for prudent use of AB at ambulatory level 	<ul style="list-style-type: none"> Main highlighted interventions were: <ul style="list-style-type: none"> - Audit and feedback - Educational meetings - Education outreach visits - Financial and healthcare systems changes - Physician reminders - Patient-based interventions - Multi-faceted intervention Singe-intervention resulted in small changes in prescribing behaviour. Patient-based interventions and physician reminders look promising 	NA	348	Included in the report
<u>Delayed prescriptions</u>	1966-2003	<ul style="list-style-type: none"> 4 RCT and 1 controlled before-after studies were included 	<ul style="list-style-type: none"> Systematic review Delayed prescription interventions for upper RTIS Output: proportion use of AB 	<ul style="list-style-type: none"> Lot of heterogeneity in the studies The included studies showed a consistent reduction in the use of antibiotic The RR for lower antibiotic usage when a delayed prescription was given ranged from 0.54 for the common cold to 0.25 for otitis media, The duration of the delay for prescriptions ranged widely from 1 to 7 days, and Tow of fours RCTs found that patients were less satisfied if they were given delayed antibiotic prescriptions. 	NA	350	Included in the report
<u>All interventions</u>	1975-2001	<ul style="list-style-type: none"> 26 studies included 	<ul style="list-style-type: none"> Systematic review 	<ul style="list-style-type: none"> Clinician Education + audit and feedback 	NA	519	Results are inconsistent



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
		<ul style="list-style-type: none"> Acute infections Outpatient setting Look for intervention to improve the selection of AB 	<ul style="list-style-type: none"> 26 studies (RCT, CBA, interrupted time series) that reported results from 33 RCT 14 trials from EUROPE, 10 USA, and other countries Output: proportion (or volume) of recommended AB prescriptions, or percent adherence to a prescribing guideline 	<ul style="list-style-type: none"> Clinician education 3 different interventions Overall, the median increase in recommended AB prescribing attributable to the intervention was 10.6% (IQR 3.4-18.2%) The median effect of interventions combining clinician education with audit and feedback was smaller than for interventions providing clinician education alone 			<p>with other studies and confounding factors are presents</p> <p>Not included in the report</p>
<u>Delayed antibiotics prescriptions</u>	1984-2017	<ul style="list-style-type: none"> Delayed antibiotic prescription (advice to delay the filling of an antibiotic prescription by at least 48 hours) 11 trials (3 from European countries) included, 3 555 patients Both at hospital (emergency department) and ambulatory level Respiratory tract infections (RTIs) 	<ul style="list-style-type: none"> Systematic review + meta-analysis Randomized Controlled Trial (RCT) included 	<p><u>1) Clinical outcome (Sore throat)</u></p> <ul style="list-style-type: none"> Pain was not significantly different for delayed and immediate AB in three studies In one study pain was reported by a higher proportion of participants in delayed AB group De la Poza et al. reported longer pain duration than participants in the immediate AB arm (n=94)⁵²⁰ One study found no evidence of difference in malaise severity, the other study detected a much higher proportion of participants with malaise on Day 3 in the delayed AB group compared to the immediate AB group (OR =16.49) Two studies found fever severity on DAY 3 to be higher in participants in the delayed group One study found that the median number of days with of fever experienced by participants in the delayed antibiotic group was one day 	NA	³⁴³	<p>Interesting but interpretation should be made carefully because there are a lot of heterogeneity in the results</p> <p>Included in the report</p>



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
				<p>longer than for the immediate AB group</p> <ul style="list-style-type: none"> In one study, the number of days with fever was not significantly different for participants in the delayed AB group <p><u>2) AB use</u></p> <ul style="list-style-type: none"> All seven studies (delayed vs immediate AB) found that AB use was significantly reduced in the delayed group Delayed AB resulted in a significant reduction in AB use compared to immediate AB prescriptions (OR 0.04, 95%CI 0.03-0.05) <p><u>3) Patient satisfaction</u></p> <ul style="list-style-type: none"> No evidence of difference between number of participants in the delayed group who were satisfied compared to the immediate AB group 			
<u>Guidelines AND Education material AND Focus group</u>	1997	<ul style="list-style-type: none"> Australia (Perth) GPs (n=112) Upper and lower respiratory tract infections, otitis media and urinary tract infections 	<ul style="list-style-type: none"> Pilot study RCT Intervention was a visit to present AB guidelines and a focus group 2 months after Output: number of prescriptions 	<ul style="list-style-type: none"> Active group prescribed significantly more recommended AB than control group (more amoxycillin (p<0.02) and doxycycline (p<0.001)) 	The total cost of antibiotics prescribed by doctors in the control group increased more than in the active group	⁵²¹	<p>Too old RCT</p> <p>Not included in the report</p>
<u>Feedback AND Educational visit</u>	1999	<ul style="list-style-type: none"> Australia (New South Wales) GP (n=157) 	<ul style="list-style-type: none"> RCT Educational programme in two steps: 1) Individual 	<ul style="list-style-type: none"> Unclear No significant difference of prescribing rate observed 	NA	⁵²²	<p>Results unclear</p> <p>Not included in the report</p>



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
<u>Educational outreach visits AND guidelines AND reminder</u>	2000-2001	<ul style="list-style-type: none"> Antwerp (Belgium) Flemish GP (n=85) Acute cough 	<ul style="list-style-type: none"> prescriber feedback 2) Educational visit Output: prescribing rate Cluster-RCT Clinical practice guideline for acute cough (by mail) Educational outreach visit Postal reminder to support its implementation Output: prescribing rate and patients' symptom resolution 	<ul style="list-style-type: none"> Differences between interventions could exist Patients in the intervention group were less likely to receive an antibiotic after our intervention compared with controls (OR adj 0.56, 95% CI 0.36-0.87) 	<ul style="list-style-type: none"> The antibiotic cost was lower in the intervention group after the intervention compared with the control group. Mean Difference (MD) adj = - Euro 6.89 (95% CI -11.77- -2.02), and compared with the pre-test MD adj (- Euro 6.11, 95% CI -9.97- -2.24) 	328	<p>Interpretation should be made carefully because some results are unclear</p> <p>Not included in the report (in the Belgian intervention chapter)</p>
<u>Education AND material communication programme AND feedback</u>	2000-2001	<ul style="list-style-type: none"> Utrecht (Netherlands) GP (n=100) Respiratory tract symptoms 	<ul style="list-style-type: none"> RCT + follow-up (15 months) ARTI-1 study Group education + Communication skills training Monitoring and feedback on prescribing rates 	<ul style="list-style-type: none"> Prescribing rates of antibiotics for respiratory tract symptoms fell by 12% compared with the control group Intervention did not change patients' degree of satisfaction After 15 months, the number of antibiotic prescriptions in the intervention group was still lower than in the period before the intervention 	NA	368	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Refere nce	Remark and Critical appraisal of review quality
			<ul style="list-style-type: none"> Education for assistants of general practitioners and pharmacists Education material for patients Output : prescription rates + satisfaction 				
<u>Multifaceted intervention</u> <ul style="list-style-type: none"> Guideline Diagnostic skills development Educational material Campaign Communication 	2000-2006	<ul style="list-style-type: none"> Israel Primary care Paediatricians (n=52) Children (n=88 000) 	<ul style="list-style-type: none"> cRCT Development of guidelines using focus group meetings, workshop, seminars and practice campaigns Output: annual AB prescription rate 	<ul style="list-style-type: none"> Decrease in the total annual AB prescription rate of children treated by the intervention physicians compared with those treated by the control physicians in the first intervention years (RR 0.76, 95% CI 0.75-0.78) The reduction crossed over all AB class but more prominent for macrolides The effect was sustained during the 4 following years 	NA	516	<p>No result by type of intervention, local guideline are not especially interesting for the Belgian context</p> <p>Not included in the report</p>
<u>Guideline AND Small-group education AND educational materials AND Feedback</u>	October 2000-March 2003 (3 times)	<ul style="list-style-type: none"> USA (16 Massachusetts communities) Parents + Physicians Focus on children 	<ul style="list-style-type: none"> cRCT (REACH trial) Output: overall number of oral AB dispensing per person-year of observation Guidelines developed by a panel of experts Materials developed using previously defined guidelines and distributed to parents and physicians Physicians received bi-monthly briefs on a topic related to AB use + visit by an educational coordinator to answer 	<ul style="list-style-type: none"> They observed a downward trend in AB prescribing, even in the absence of intervention (?) The intervention was responsible for a 4.2% decrease among children aged 24 to < 48 months and a 6.7% decrease among those aged 48 < 72 months (no impact on children 3 -24 months) The intervention effect was greater among Medical-insured children and for broad-spectrum agents 	NA	523	<p>Intervention not useful for the Belgian's context</p> <p>Not included in the report</p>



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
			question and provide additional material <ul style="list-style-type: none"> Parents received mailed twice each winter, website available, posters, stickers,... distributed Stickers also distributed to pharmacists, etc. Training (year 3) of local child care center directors and teachers 				
<u>New reimbursement policy (restricted utilization to defined subgroups)</u>	2005	<ul style="list-style-type: none"> Canada (Alberta) Albertans ≥ 65 years 170 247 'outpatients' Quinolones 	<ul style="list-style-type: none"> New policy = Restricting the use of quinolones to defined subgroups of patients with common infections including urinary tract infection (UTI), upper respiratory infection (URTI), acute exacerbation of chronic bronchitis (AECB) and community acquired pneumonia (complete and fax a paper-based prior authorization from to Alberta Blue Cross before the prescription would be reimbursed) (OSA programme). Some GPs were voluntary enrolled and some other not. Observational study Output: <ul style="list-style-type: none"> Rate of quinolones use 	<ul style="list-style-type: none"> No significant change in monthly rate of all quinolone use (-3.5%, 95% CI -5.5-1.4, prescriptions per 1000 index visits) following implementation of the OSA programme Significant level change in the rate of quinolone AB use for UTI (-33.6, 95% CI -23.8--43.4) and upper respiratory tract infection (-16.1, 95% CI -11.6--20.6) prescriptions per 1000 index visits Prescriptions of quinolone were significantly more consistent with formulary guidelines before and after the implementation of OSA programme (42.5% vs. 58.5%, $p=0.002$) No change in hospitalization, mortality or use of physicians services after implementation of OSA programme 	NA	380	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
			<ul style="list-style-type: none"> - Hospitalization, use of physician services • Outcome: - Mortality 				
<u>CRP Point-of-care test AND Communication Skills</u>	2005-2006	<ul style="list-style-type: none"> • Netherlands • GPs (n=40) • Lower respiratory infection 	<ul style="list-style-type: none"> • RCT • CRP Point-of-care test • IMPACT3 study • Communication skills (11 key tasks) • Output: antibiotic prescriptions rate 	<ul style="list-style-type: none"> • CRP test group prescribed AB to 31% of patients compared with 53 % in the no test group (p=0.02) • Clinicians in the combined group prescribed antibiotics to 23 % of patients • Patients' recovery and satisfaction were similar in both group 	NA	372	Included in the report
<u>CRP Point-of-care test OR Communication Skills</u>	2005-2006	<ul style="list-style-type: none"> • The Netherlands (South) • GPs (n=20) • Low RTIs 	<ul style="list-style-type: none"> • RCT • CRP testing as point-of-care • Communication skills training • Output: prescribing rate, consultation rate 	<u>CRP</u> <ul style="list-style-type: none"> • GP in the CRP test group prescribed significantly fewer antibiotics than those in the no test group (31% vs. 53%, p<0.01) <u>Communication</u> <ul style="list-style-type: none"> • GP in the communication skills training group prescribed significantly fewer antibiotics than those in the no training group (27% vs. 54%, p<0.01) • No significant difference in re-consultation rate 	NA	512	Sample size very limited. Not included in the report
<u>CRP Point-of-care test AND/OR Communication skills</u>	2005-2007; 2010	<ul style="list-style-type: none"> • Netherlands • GPs (n=20) • Respiratory infections patients (n=379) 	<ul style="list-style-type: none"> • cRCT + follow-up (3.5 years) • Output: number of visits for respiratory infections per patient year (PPPY) + percentage of the episodes for which patients were treated with AB during follow-up 	<u>Overall</u> <ul style="list-style-type: none"> • Family physician's use of CRP point-of-care testing and/or training in enhanced communication skills did not significantly affect office visit rates related to respiratory tract infections <u>Communication</u>	NA	371	Results seem contradictory with IMPACT -3 study results Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
				<ul style="list-style-type: none"> Patients managed by a physician who had training in enhanced communication skills received an AB prescription in 26.3% of all episodes during the 3.5 years follow-up, whereas patients managed by physician who did not have training in communication skills received an AB prescription for 39.1% of all episodes ($p=0.02$) 			
<u>Clinical decision support device</u>	2006-2010	<ul style="list-style-type: none"> USA Ambulatory care Acute bronchitis and upper respiratory tract infection 	<ul style="list-style-type: none"> Case-control study (not clear?) Clinical decision support (which includes electronic warning systems or alerts to highlight potential contraindications for prescriptions ordered) Outcome: AB prescription rate 	<ul style="list-style-type: none"> Use of decision support was associated with a 19% lower likelihood of receiving an antibiotic prescriptions 	NA	378	Included in the report
<u>Multifaceted interventions:</u> <ul style="list-style-type: none"> Seminar reflecting on practices Education Practising consulting skills in routine care 	2007-2008	<ul style="list-style-type: none"> Wales (United Kingdom) 263 clinicians included 	<ul style="list-style-type: none"> RCT 'STAR' training Various learning methods and topics (reflection on own practice, provision of new research evidence, etc.) 	<ul style="list-style-type: none"> Reduction of 4% in overall oral AB prescription in practitioners who received the STAR training 	NA	373	Included in the report
<u>CRP Point-of-care test</u>	2007-2008	<ul style="list-style-type: none"> Netherlands Patients ($n=258$) + GP ($n=32$) involved RTI 	<ul style="list-style-type: none"> RCT Output: AB use after the index consultation; AB use during the 28-day 	<ul style="list-style-type: none"> Patients in the CRP-assisted group used fewer AB (43.4%) than control patients (56.6%) after the index consultation (RR 0.77, 95% CI 0.56-0.98) 	NA	370	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
			follow-up, satisfaction patients • Outcome: clinical recovery	• This difference remains significant during the follow-up (28 days) • Recovery was similar in both groups • Satisfaction with care was higher in patients managed with CRP assistance (p=0.03)			
<u>Educational program</u>	2010-2011	• Quebec, Canada • Family physicians • Respiratory infections	• Cluster-RCT • 'DECISION 2' program • 2-hour online tutorial followed by a 2-hour interactive seminar about shared decision-making. • Output: proportion of patients who decided to use antibiotics immediately after consultation	Not clear	NA	⁵²⁴	Results unclear and did not report an objective measure of antibiotic use by patients. Not included in the report
<u>Tool-assisted decision support</u>	January 2010-May 2011	• UK, London • Nursing home (n=30), 1 832 nursing beds • 1 628 residents included (GPs and nurses)	• Prospective cluster randomized control pilot study • Pre-printed from: - Part A: Initiation of 'Treatment' was to be completed before administration of the first dose and - 'Part B: Review of Treatment' commenced 48-72 h after starting treatment	• There was a significant decrease of 4.9% (3.25 DRD) in the intervention group (95% CI 1.0-8.8, p=0.02) compared with a significant increase of 5.1% (2.24 DRD) in the control group (95% CI 0.2-10.2, p=0.04)	NA	³⁸¹	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
			<ul style="list-style-type: none"> - Both parts were divided into subsections or 'good practice points' in relation to antimicrobial prescribing, administration and monitoring in line with prior Department of Health (England) recommendations • Output: mean number of prescriptions per 100 residents and defined daily doses per 1000 residents per day (DRD). 				
<u>Multifaceted interventions</u> <ul style="list-style-type: none"> • Training in the use of CPR test at point care • Communications skills • Interactive booklet tool • Structured meeting 	2011	<ul style="list-style-type: none"> • Belgium (Antwerp), Spain (Barcelona), Wales (Cardif), Poland (Lodz), UK (Southampton), Poland (Szczecin), Netherlands (Utrecht), Spain (Spanish Society of Family Medicine) • Clinicians and general practices • 259 practices • 6 771 patients • Lower RTIs 	<ul style="list-style-type: none"> • RCT • Training in the use of CPR test at point care (on internet + on-site training with the QuickRead CRP kits) • Training in enhanced communication skills • Interactive booklet provided • Structured meeting on prescribing issues • GRACE study • Output: proportion of AB use 	<ul style="list-style-type: none"> • Both types of training were associated with notable reduction in antibiotic prescribing rates, but the two training methods combined had the greatest effect 	NA	323	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
<u>CRP Point-of-care test</u>	July 2013-April 2014	<ul style="list-style-type: none"> Two out-of-hours services in Oxfordshire (UK) 54 acutely ill children included in the RCT 12 parents, 5 GPs and 2 study nurses included in the qualitative study 	<ul style="list-style-type: none"> RCT and Qualitative study Output: AB use, re-hospitalisation, additional testing in primary care, re-consultation, acceptability of the CRP test 	<ul style="list-style-type: none"> There was no statistically significant difference in any outcome between those tested or not tested with CRP point-of-care In the 10-days follow-up period, children randomised to CRP testing received significantly more AB prescriptions ($p=0.023$) Parents reported no major concern about the test Nurses also reported that children accepted the test, and there were no problems with pain or discomfort The GPs and some parents emphasised that a CRP result should be part of an overall assessment >80 mg/L=giving AB. However safety of such strategy should be assessed before widespread implementation, as studies suggest that serious infections can be present in children with CRP levels as low as 5mg/L, especially in the early stages of the illness 	NA	374	Included in the report
<u>Multifaceted intervention:</u> <ul style="list-style-type: none"> Guideline Audit Reminder Delayed prescription Education material for patients (multimedia application) 	July 2013-March 2014	<ul style="list-style-type: none"> Ireland 71 GPs 3 314 consultations UTI 	<ul style="list-style-type: none"> Cluster randomized trial 'SIMPlE study' Interventions: <ul style="list-style-type: none"> 1) All GPs participated to a 'coding workshop' during which the study was explained and the importance of consultation coding for the audit reports 2) Arm A received info on national guidelines for 	<ul style="list-style-type: none"> An absolute increase of 20% of AB prescribing according to guidelines was achieved for practices in the interventions arms, and patients attending an intervention practice were twice likely to receive a prescription for a first-line antimicrobial for their UTI as those attending control group Improvements in guideline-based prescribing were sustained at 5 months after the intervention 	NA	360	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
			<p>AB use and result from the first audit report, Arm B received same info as arm A, along with additional evidence to support delaying AB prescriptions for suspected UTI. A reminder outlying guideline appeared when UTI code was used for both arm A & B. For Arm B, reminder also urged the physician to consider delayed prescription. Controlled group only received a workshop focused on coding practices</p> <ul style="list-style-type: none"> - 3) A multimedia application was introduced (game for children, etc.). Controlled group received the application after 6 month and the audit report - 4) A follow-up period of 5-month of passive data collection was performed • Output: proportion of prescription for recommended first-line AB for suspected UTI 				
<u>Feedback</u>	October 2013-	<ul style="list-style-type: none"> • Switzerland • Nationwide 	<ul style="list-style-type: none"> • RCT • Physicians in the intervention group 	<ul style="list-style-type: none"> • Physicians receiving feedback prescribed the same amount of antibiotics to all patients as 	NA	362	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
	July 2015	<ul style="list-style-type: none"> Selected the 2 814 top AB prescribers of Switzerland in primary care 	<ul style="list-style-type: none"> received a quarterly updated personalized prescription feedback. Physicians in the control group received no material Output: prescribed DDD of any type of antibiotics to any patient per 100 consultations (DDD/100c) in the first year 	physicians without feedback. No significant impact of the intervention			
<u>Feedback Educational material</u> & <u>Feedback Educational material</u>	2014-2015	<ul style="list-style-type: none"> England National level (top 20% AB prescription practices) GPs (n=1 581) 	<ul style="list-style-type: none"> RCT Intervention: Feedback through clinician-focused letter (constructed on three main concepts from behavioural sciences: social norm comparison, addressed from a high-profile figure and presented three feasible actions to reduce unnecessary AB use) and/or patients-focused posters and leaflets Output: rate of AB items dispensed per 1000 population 	<u>Feedback</u> <ul style="list-style-type: none"> The rate of AB items dispensed per 1000 population was significantly lower in the feedback intervention group (126.98, 95% CI 125.68-128.27) than in the control group (131.25, 95% CI 130.33-132.16) <u>Educational material</u> <ul style="list-style-type: none"> Education material for patients had no significant impact on AB prescription rate <u>Feedback & Educational material</u> <ul style="list-style-type: none"> Both interventions have also a significant impact on prescription rate (132.92, 95% CI 130.85-134.98) but not better than feedback alone 	<ul style="list-style-type: none"> They estimated that feedback intervention created a £92 356 saving in direct prescribing costs for the public sector 	363	Included in the report
<u>CRP Point-of-care test</u>	2014	<ul style="list-style-type: none"> Six trials (3 RCT – 3 cRCT) with a low to moderate risk of bias are included (3 284 	<ul style="list-style-type: none"> Systematic Review (quality of the evidence sified as moderate) Focused on acute respiratory infections Output: AB use 	<ul style="list-style-type: none"> Overall a reduction in the use of AB treatments was found in the CRP group versus standard of care (RR 0.78, 95% CI 0.66-0.92; I² 68%), however given the high level of heterogeneity between studies, the pooled effect and the conclusions 	NA	353	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
		participants; 139 children) • Includes ^{372; 370; 323}	• Outcome: duration of recovery from infection; complications including the number of re-consultations, hospitalisations and mortality	should be interpreted with caution. Authors concluded that the heterogeneity was caused by the study design because when they did the meta-analysis by subgroups, heterogeneity disappeared. RCT: RR 0.90, 95% CI 0.80-1.02, I ² 5%. cRCT: RR 0.68, 95% CI 0.61-0.75, I ² =0% • No difference between using a CRP point-of-care test and standard care in clinical recovery was observed. • Increase in hospitalisations in the CRP group (but based on few events – low evidence) • No death reported			
<u>Multifaceted interventions</u> • Communication training • Electronic decision support tool • Feedback	2015 (?)	• Netherlands & GPs & pharmacists (n=77), i.e. PharmacoTherapy Audit Meeting (PTAM) groups • RTIs	• cRCT • Communication skills training (+ on delayed prescription) • Implementation of antibiotic prescribing agreements in GP Electronic Prescription system • Feedback (using figures) • Output: difference in the number of RTI-related AB prescriptions	• For patients of 12 years and older, the drop in the number of AB prescription was significantly larger in the intervention group (-27.8 per 1000 patients) than in the control group (-7.2 per 1000 patients, p<0.05) • No effect on children <12 years	NA	³⁶⁹	Interesting and useful study for the report. PTAM is interesting to investigate as well as communication skills on delayed prescription, feedback using figures and AB agreement directly included in electronic prescription system Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Refere nce	Remark and Critical appraisal of review quality
<i>Stewardship to both hospital and ambulatory care level</i>							
<u>e-Audit and feedback</u>	1946-2016	<ul style="list-style-type: none"> Primary care & hospital context Healthcare professional 9 studies included (all from developed countries) 829 health care professionals 81 700 patients 	<ul style="list-style-type: none"> Systematic Review of audit and feedback intervention + meta-analysis RCTs included Audit and feedback defined as the provision of clinical performance summaries Output: effectiveness of e-Audit and feedback interventions for clinical practice and hospital settings 	<ul style="list-style-type: none"> Electronic Audit and Feedback highly heterogeneous; average effect unreliable 	NA	525	Lot of heterogeneity in the included studies. Effectiveness cannot be demonstrated Not included in the report
<u>Communication online tool</u>	1996-1997	<ul style="list-style-type: none"> USA Paediatricians (n=10) 	<ul style="list-style-type: none"> Prospective observational study Online commentary has potential as a communication technique that physicians could use to resist pressure for inappropriate antibiotic prescriptions 	<ul style="list-style-type: none"> 'No problem', online commentary exclusively antibiotics were prescribed 45% of the time 'Problem' online commentary, antibiotics were prescribed 66% of the time 	NA	526	Results should be interpreted carefully as few paediatricians were included Not included in the report
<u>Educational interventions</u>	2001-2011	<ul style="list-style-type: none"> 78 studies included= primary-care (n=47) and hospital settings (n=31) 	<ul style="list-style-type: none"> Systematic review of educational interventions RCT and observational studies included Target population: physicians and/or pharmacists 	<ul style="list-style-type: none"> More papers on educational interventions in physicians than pharmacists Respiratory disorders were the diseases targeted by most studies (mainly in primary care) Multiple and Active interventions were more effective 	NA	351	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
			<ul style="list-style-type: none"> Output: adherence to guidelines and total AB prescribed 	<ul style="list-style-type: none"> Few studies conducted follow-up after the intervention has ended and cost-effectiveness analysis Few studies analysed improvement in bacterial susceptibility as outcome 			
<u>Tool kit</u>	2006-2012	<ul style="list-style-type: none"> The Netherlands 	<ul style="list-style-type: none"> Observational study 	<ul style="list-style-type: none"> Compare the local SWAB-ID-based and non-SWABID-based antimicrobial guides for comprehensiveness and compliance with the national antimicrobial guidelines. By the end of 2012, 40% of Dutch hospitals used a local customised version of SWAB-ID and 60% did not join the SWAB-ID initiative and continued to fully design their own guide. The study also investigated 50 antimicrobial guides and reported that the local non-SWAB-ID based guidelines were significantly less comprehensive (64 vs 90%, $p < 0.001$) and less followed national guidelines than SWAB-ID-based guides (46 vs. 70%, $p < 0.001$). 	NA	393	Included in the report
<i>Mass (National) intervention activities</i>							
<u>National program against antibiotic resistance</u>	1995-2004	<ul style="list-style-type: none"> Sweden 	<ul style="list-style-type: none"> Follow-up study STRAMA program 	<ul style="list-style-type: none"> Between 1995 and 2004, antibiotic use for outpatients decreased from 15.7 to 12.6 DDD per 1000 inhabitants per day and from 536 to 410 prescriptions per 1000 inhabitants per year 	NA	382	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
<u>National AB stewardship strategy</u> <ul style="list-style-type: none"> Public service campaign entitled 'Les antibiotiques c'est pas automatique' guideline education ... 	2002-2007	<ul style="list-style-type: none"> France 453 407 458 individual reimbursement data records Population + GPs + paediatrician 	<ul style="list-style-type: none"> Times series analysis Output: rate of antibiotic prescriptions 	<ul style="list-style-type: none"> The total number of antibiotic prescriptions per 100 inhabitants changed by -26.5% (95% CI --33.5-19.6%) over 5 years The decline occurred in all 22 regions of France and affected all antibiotic therapeutic classes except quinolones The greatest decrease, -35.8% (95% CI -48.3%--23.2%), was observed among young children aged 6-15 years. https://www.youtube.com/watch?v=Rzrj9adSFIQ; https://www.youtube.com/watch?v=ydg6zY4yhEw; https://www.youtube.com/watch?v=dXNon2bCWxo. 	From 2002 and 2008, the cost of the campaign was estimated to be 500 000 000 euros, i.e. 1.4 euro per inhabitant per year. Between 2002 and 2007, direct savings related to decreased antibiotic use was estimated to be 850 000 000 euros; i.e. 2.80 euros per inhabitant per year	³⁷⁷	Included in the report
<u>Quality indicators</u>	2004 & 2009	<ul style="list-style-type: none"> 32 European countries 	<ul style="list-style-type: none"> ESAC quality indicators are constructed on use criteria and aim to make comparisons between European countries and to evaluate changes in quality of AB use Output: to evaluate changes in quality between 2004 and 2009 	<ul style="list-style-type: none"> ESAC indicators have resulted in improved antibiotic prescribing in several European countries between 2004 and 2009 	NA	³⁸³	Included in the report
<u>National AB stewardship strategy</u>	2006-2011	<ul style="list-style-type: none"> Scotland 1 289 929 hospital 	<ul style="list-style-type: none"> Time-series analysis and quasi-experimental 	<ul style="list-style-type: none"> During antibiotic stewardship, use of 4C and macrolide antibiotics fell by 	NA	³⁷⁶	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
<ul style="list-style-type: none"> • Restriction use of 4C (cephalosporins, co-amoxiclav, clindamycin and fluoroquinolones) and macrolides AB • Hand hygiene campaign • Hospital environment inspection • MRSA admission screening 		admissions and 455 508 adults registered in primary care	<ul style="list-style-type: none"> • Intervention is a national stewardship strategy • Output: hospital or community MRSA prevalence density & AB use in DDD per 1000 occupied bed days (hospital) or per 1000 inhabitant per day (community) 	47% in hospitals and 27% in the community <ul style="list-style-type: none"> • MRSA prevalence density was reduced by 50% in hospitals and by 47% in community 			
<u>Restricted antibiotics and prior-authorization</u>		<ul style="list-style-type: none"> • Canada (Alberta) • GPs • 170 274 population 	<ul style="list-style-type: none"> • Time-series analysis • The policy consisted of restricting the use of quinolones to defined subgroups of patients with common infections including urinary tract infection (UTI), upper respiratory infection (URTI), acute exacerbation of chronic bronchitis (AECB) and community acquired pneumonia • Output: use of quinolones 	They observed no significant change in monthly rate of all quinolone use (-3.5%, 95% CI -5.5-1.4; prescriptions per 1000 index visits) following implementation of the program. However they still noted a significant level change in the rate of quinolone antibiotic use for UTI (-33.6, 95% CI -23.8--43.4) and URTI (-16.1, 95% CI -11.6--20.6) prescriptions per 1000 index visits. Prescriptions of quinolone were also significantly more consistent with formulary guidelines before and after the implementation of the intervention (42.5% vs. 58.5%, p=0.002) but no change in	NA	380	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
				hospitalization, mortality or use of physicians services after implementation of the program was observed			
<u>Mandatory ASP at hospital</u>	2014	<ul style="list-style-type: none"> • UK, France, USA • Hospital AB stewardship 	<ul style="list-style-type: none"> • Synthesis of national requirement for hospital ASP 	<ul style="list-style-type: none"> • There are differences in the legislative requirements and the development and implementation of hospital ASP among countries • No mandatory AB stewardship policy in USA at hospital level • Additional results are available in the report 	NA	355	<p>Very useful to describe the situation in France</p> <p>Included in the report</p>
<u>National AB stewardship strategy</u>	2015	<ul style="list-style-type: none"> • UK 	<p>In 2013, a five-year national strategy for tackling antimicrobial resistance was published in the UK. The initiatives were:</p> <ol style="list-style-type: none"> 1) Making it mandatory for hospitals to report all cases of bacteraemia caused by <i>S.aureus</i> and <i>Escherichia coli</i>, and all cases of <i>Clostridium difficile</i> infection 2) Establishing an expert advisor committee on antimicrobial resistance and healthcare-associated infections to advice on actions needed to tackle the problem of resistance 3) Establishing the English Surveillance Programme for Antimicrobial Usage and Resistance (ESPAUR) 4) Updating relevant legislation, in particular the 	<p>Implemented measures were:</p> <p>In primary care:</p> <ul style="list-style-type: none"> - Quality premium to reward clinical commissioning groups for improvements in the quality of services + 3 workshop for the clinical commissioning groups - Target toolkit, an on-line antimicrobial stewardship resources designed to help influence prescribers' and patients' personal attitudes, social norms and perceived barriers to optimal AB prescribing. Toolkit includes a self-assessment checklist, training resources, patient information leaflets, etc. <p>In secondary care:</p> <ul style="list-style-type: none"> - Antimicrobial stewardship toolkit, 'smart then focus' guidance strategy for hospitals - Validation of antimicrobial use data. For the first time, data on AB use were published in 2014 by region <p>In both:</p>	NA	527	<p>Interesting to describe the UK strategy but did not include evaluation</p> <p>Not included in the report</p>



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Reference	Remark and Critical appraisal of review quality
			<p>health and social care Act 2008 to include a new section on the role of infection in optimizing antimicrobial use and reducing antimicrobial resistance</p> <p>5) Publication of a strategy, comprising seven areas for action:</p> <ul style="list-style-type: none"> Improving infection prevention and control practices Optimizing prescribing through stewardship Improving professional education, training and public engagement Developing new drugs, treatment and diagnostics Better access to and use of surveillance data Better identification and prioritization of AMR research needs Strengthened international collaboration 	<ul style="list-style-type: none"> National Institute for Health and Care Excellence published guidance on antimicrobial stewardship A multi-professional group published national antimicrobial prescribing and stewardship competencies in 2014 			
<u>Mass Campaigns</u> <u>Regulation</u> <u>package size</u>	2016	<ul style="list-style-type: none"> Netherlands, France, Poland, Malta, Spain 	<ul style="list-style-type: none"> Synthesis of : <u>Mass campaigns</u> Mass Media Campaign Antibiotic Awareness DAY <u>Governmental regulations on package size</u> 	<u>Mass campaign:</u> <ul style="list-style-type: none"> In France, overall AB use fell by 10.7 % during a national mass media campaign that lasted from 2002 until 2010. Campaign included: TV & radio spots, slogans, information booklets, and leaflets ³⁷⁷ Poland celebrates an AB Awareness Day each year on the 18th November. Different stakeholders are engaged: 	NA	³⁵⁴	Included in the report



Intervention	Date Data collection	Country & Target group	Design and outcome(s)	Results primary outcome	Economic evaluation	Refere nce	Remark Critical appraisal of review quality
				<p>scientific societies, outpatient clinics, public transport, radio, the press, etc. Scientific conferences are also organised. In 2009, a questionnaire study revealed that about 30% of the people who were informed about the rational use of AB stated that they adapted their AB use</p> <ul style="list-style-type: none"> - In Malta, educational and motivational interventions led to more responsible use of AB <p><u>Package size:</u></p> <ul style="list-style-type: none"> - In Spain, AB use was significantly decreased after adjusting the package size of oral AB. After this campaign fewer respondents obtained AB without doctor's prescription. According to ECDC ESAC-Net surveillance data, this had a significant impact on the AB use 			

AB: Antibiotic; ASP: Antibacterial Stewardship Program; CBA: Control Before After; CCT: Control Clinical Trial; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-Reactive Protein; DDD: Defined Daily Dose; DOS: days of therapy; DRD: Defined daily doses per 1000 Residents per Day; GP: General Practitioner; IQR: InterQuartile Range; ITS: Interrupted Time Series; LOS: Length Of Stay; MIT: Multidisciplinary Infectious diseases Team; MRSA: Meticillin-Resistant Staphylococcus Aureus; NA: Not Available; QI: Quality Indicator; OR: Odds Ratio; PCT: Procalcitonin; PTAM: PharmacoTherapy Audit Meeting; RR: Risk Ratio; RCT: Random Controlled Trial; RTIs: Respiratory tract infections; UTI: Urinary Tract Infection



APPENDIX 4. QUESTIONS USED IN THE INTERVIEW GUIDE

Appendix 4.1. Key questions for interviewees from the human (ambulatory and hospital) sector

- What are the evolutions that happened in the last years regarding AB use?
- What are the key factors for this evolution?
- What are key factors that influence human antibiotic use?
- What additional factors or interventions could have a significant effect on human AB use?
- Which interventions could work? How can we realize them? How can we implement them?
- What are the key elements of existing policy to regulate human AB use? What works well? What is missing?
- What would be the key elements of a successful communication and information strategy? (awareness campaigns, guidelines, education/training,...)
- How can financial incentives be used to influence AB use?
- Is the current regulatory framework sufficiently binding?
- What are key elements in the coordination between hospital care, ambulatory care and the veterinary sector?
- How do you see the role of pharmaceutical companies?
- If you would have unlimited authority, what would be your key recommendations to improve AB policy in Belgium?

Appendix 4.2. Additional questions for interviewees from the ambulatory sector

- What do you think about the current guidelines on AB use? Is it clear which guidelines should be applied? Are the guidelines easy to access? Are they clear, practical, useful?
- How well informed are General Practitioners and other first line health physicians about AB use and antimicrobial resistance in general?
- How would you assess the current awareness campaigns, in terms of planning, reach, timing, resources, impact?
- How would you assess current education/training programmes for prescribers: are they practical, sufficient, effective?
- How would you assess current monitoring of GPs with regard to AB use? Should it be improved? How?
- Would it be useful to introduce a system of certification on AB use among GPs? Which institution should back it up?
- Would it be useful to introduce a system of benchmarking for GPs? Which institution should back it up?
- Could it be useful to introduce a financial trigger for GPs to improve their prescription behavior? What kind of financial trigger would that be?
- Should first line prescribers be subject to a more stringent regulatory framework?
- What do you think about the role of pharmaceutical companies in influencing AB prescription behavior? Have you ever been contacted by one?
- If you could make three important changes in AB-policy in Belgium, what would they be?



Appendix 4.3. Additional questions for interviewees from the hospital sector

- What do you think about the current guidelines on AB use? Is it clear which guidelines should be applied? Are the guidelines easy to access? Are they clear, practical, useful?
- How would you assess the current awareness campaigns in terms of planning, reach, timing, resources, impact?
- How would you assess current education/training programmes for prescribers: are they practical, sufficient, effective?
- Do you participate in PPS (Point Prevalence Surveys)? Who is the organizing entity (ECDC or "Global")? How would you assess PPS? Is it useful, effective, well organized?
- Do you participate in audits on prophylactic and/or therapeutic use of AB?
- AB Stewardships: how well do Antibiotic Policy Groups function in your institution? Could this be improved? How?
- How would you assess the current financial triggers that are being used to reduce AB use in hospitals?
- How would you assess the surveillance of AB use in Belgium in general? What can be done to improve it?
- If you could make three important changes in AB-policy in Belgium, what would they be?

Appendix 4.4. Key questions for interviewees from the veterinary sector

- What are the evolutions that happened in the last years regarding AB use?
- What are the key factors for this evolution?
- What are key factors of animal antibiotic use?
- What additional factors or interventions could have a significant effect on animal AB use?
- Which interventions could work? How can we realize them? How can we implement them? What are key elements of the existing policy to regulate animal AB consumption? What works well? What is missing?
- If you would have unlimited authority, what would be your key recommendation to improve AB policy in Belgium?
- Within the context of AB, what do you consider as crucial relationships?
- What are the benefits of using AB? Please elaborate in the light of prevention and treatment?
- Is all AB use the same in context of AMR?

Additional questions:

- What is the influence of the livestock species on the whole picture around AB use and AMR?
- What is your take on the contribution from the veterinary sector in the rise of AMR compared to the human sector?
- What are the stages of the prescription process? When do you ask a veterinary doctor to consider AB treatment?
- What drives the need of AB treatment in animal farms? What have you learned from your experience?
- Is it clear what guidelines should be applied? Are you familiar with the AMCRA guidelines (cfr. formularia)? Please elaborate.



- Is there a risk associated with so called prudent AB use? What could be the consequences? Do you have suggestions for mitigation strategies?
- What percentage of the veterinary income is coming from AB sales? How did it evolve historically?
- What are your current reporting obligations? Are you aware of any changes that will happen in the (near) future?
- Are there financing incentives to be considered to lower the use of AB?
- Could it be useful to introduce a financial trigger for veterinary doctors to improve their prescription behavior? What kind of financial trigger would that be?
- How would you assess current monitoring of veterinary doctors with regard to AB use? Should it be improved?
- Would it be useful to introduce a system of benchmarking for veterinary doctors? Which institution should back it up?
- What could be the potential of certifications such as Certus?
- Where do you get your knowledge about AB and AMR?
- What is your take on the relationship between veterinarian and pet owner in the context of AB prescription?



APPENDIX 5. SYSTEMS MAP

Appendix 5.1. Concepts

Table 56 lists all concepts included in the systems map, organised per cluster and in alphabetical order.

Table 56 – Concepts included in the systems map

Concept	Cluster
AB prescription for pets by APs	AP-patient relationship
Access to patient medication history	AP-patient relationship
Access to and correct use of rapid diagnostic aids	AP-patient relationship
AP ability to communicate with patients on AB effects	AP-patient relationship
Assumed patient demand for AB	AP-patient relationship
Cost to patient of antibiotics	AP-patient relationship
Degree to which patients trust their medicines rather than own healing resources	AP-patient relationship
Emergency visits in ambulatory and hospital car	AP-patient relationship
Emotional loading of patient framing of common complaints	AP-patient relationship
Frequency of consultation	AP-patient relationship
Handover between hospital and AP	AP-patient relationship
Impact of fee for service reimbursement	AP-patient relationship
Likelihood of AB prescription by other APs	AP-patient relationship
Obligation of MD certificate for one-day sick leave	AP-patient relationship
Patient knowledge of common complaints	AP-patient relationship
Patient out-of-pocket expense per consultation	AP-patient relationship
Patient treatment compliance	AP-patient relationship
Patient uncertainty about health outcomes	AP-patient relationship
Patient AB Auto-medication	AP-patient relationship
Personal character of relationship between patient and AP	AP-patient relationship
Practitioner authority as perceived by patients	AP-patient relationship



Concept	Cluster
Pressure on citizens to perform	AP-patient relationship
Propensity of APs to avoid short-term patient risk	AP-patient relationship
Self-confidence of AP	AP-patient relationship
Sense of responsibility of parents towards children	AP-patient relationship
Time available for consultation	AP-patient relationship
Weight of AB consumption culture	AP-patient relationship
Ability to frame positive, empowering messages	Campaigns
Ability to reach citizens at an early age	Campaigns
Ability to reach indifferent segment of target audience	Campaigns
Access to nationwide media	Campaigns
Access to specialised expertise to design sensitisation campaigns	Campaigns
Cultural sensitivity of campaigns	Campaigns
Effectiveness of pharmacies as communication gateways	Campaigns
Fatigue due to AB sensitisation messages	Campaigns
Funding of campaigns	Campaigns
Persistence of sensitisation campaigns	Campaigns
Quality of impact assessments of campaigns	Campaigns
Timeliness of sensitisation campaigns	Campaigns
(Assertiveness of) Patient demand for ABs	Core
Ability to adjust packaging size to treatment	Core
AB prescribing-related economic interest of veterinarians	Core
Antimicrobial resistance	Core
Appropriateness of Animal AB consumption	Core
Appropriateness of human AB Consumption	Core
Availability of old ABs	Core
Availability of cost-efficient profitable alternative treatments	Core



Concept	Cluster
Coherence of AB policy	Core
Effectiveness of AB policy	Core
Effectiveness of sector's autoregulation	Core
Effectiveness of sensitisation campaigns	Core
Effectiveness of AB stewardship teams in hospitals	Core
Effectiveness of implementation of AB prescribing guidelines	Core
Effectiveness of intersectoral coordination	Core
Enforceability of regulation of vet AB use	Core
Extent of human migratory flows	Core
Farmers' receptiveness to guidelines for prudent AB use	Core
Patient understanding of effects of AB use	Core
Practitioner expertise regarding prudent AB use	Core
Presence of AB in the environment	Core
Pressure on profitability	Core
Price of ABs	Core
Prudence of AB prescription for humans	Core
Prudence of veterinary AB prescription	Core
Readiness of APs to question AB prescribing behaviour	Core
Risk of disease	Core
Strength of historical recommendations for use of AB	Core
Strength of AP independence in relation to patient	Core
Use of appropriate AB	Core
Vet's receptiveness to AB prescribing guidelines	Core
Volume of AB in waste water streams	Core
Weight of high volume prescription culture	Core
Willingness of feed companies to support AB auto-regulation	Core
AB as convenient, accepted reinforcement of expert status	Expertise and Reflexivity



Concept	Cluster
Ability to impose restrictions on 'empirical prescription'	Expertise and Reflexivity
Access to hospital-led infection prevention networks	Expertise and Reflexivity
Access to trusted sources of scientific expertise	Expertise and Reflexivity
Age of AP	Expertise and Reflexivity
AP understanding of detrimental effects on individuals and populations of long-term AB use	Expertise and Reflexivity
Availability of tailored epidemiological data	Expertise and Reflexivity
Clinical interest of AB to medical practitioners	Expertise and Reflexivity
Cross- fertilisation between human and veterinary expertise	Expertise and Reflexivity
Expertise/ basic education of medical practitioners (MPs)	Expertise and Reflexivity
Financial incentives to APs to reduce AB prescription	Expertise and Reflexivity
Fragmentation of infectiology teaching base	Expertise and Reflexivity
Incentives associated to individual prescription profiles	Expertise and Reflexivity
Incentives via accreditation for 'life long learning'	Expertise and Reflexivity
Influence of AB prescription behaviour of senior peers	Expertise and Reflexivity
Information overload of medical practitioners (MPs)	Expertise and Reflexivity
Possibility to have personalised, authoritative feedback on AP AB prescribing behaviour	Expertise and Reflexivity
Possibility to receive feedback and discuss best practices with peers (incl. through LOKs – GLEMs)	Expertise and Reflexivity
Practitioner acceptance of formal audits	Expertise and Reflexivity
Practitioner identification with expert status (ego)	Expertise and Reflexivity
Practitioners' insistence on therapeutic freedom	Expertise and Reflexivity
Prescription incentives from AB producers	Expertise and Reflexivity
Quality and availability of information through LOKs – GLEMs (APs)	Expertise and Reflexivity
Quality of academic training on prudent AB prescription	Expertise and Reflexivity
Use of electronic prescription system to collect AB prescribing data, incl. diagnosis	Expertise and Reflexivity
Years of practice	Expertise and Reflexivity
AB auto- medication	Farmer



Concept	Cluster
AB treatment withdrawal time	Farmer
Access to antibiotic use counseling	Farmer
Attractiveness of quality labels	Farmer
Availability of benchmarking	Farmer
Degree to which livelihood depends on farming	Farmer
Farmer autonomy in production model	Farmer
Farmers' knowledge of AB pharmacology	Farmer
Government support for prudent AB use	Farmer
Impact of resistant pathogens on farmer's health and business	Farmer
Level of farmer's education	Farmer
Likelihood of continuation of farm	Farmer
Safety and effectiveness of 3d and 4th gen. ABs	Farmer
Veterinarians' communication skills	Farmer
Access to AB prescribing guidelines	Guidelines
Accessibility and visibility of BAPCOC website	Guidelines
Coherence amongst national guidelines	Guidelines
Coherence between national and internal guidelines	Guidelines
Cross- therapeutic integration of AB guidelines	Guidelines
Financial incentives based on benchmarking of prescription behaviour	Guidelines
Funding for guideline development	Guidelines
Independence from industry funding	Guidelines
International coherence of AB guidelines	Guidelines
International consensus on list of critically important ABs	Guidelines
Involvement of pharma sector in guideline development	Guidelines
Perceived legitimacy of AB prescribing guidelines	Guidelines
Possibility of pharma co to contribute to guideline development	Guidelines
Possibility of practitioners to contribute to guideline development	Guidelines



Concept	Cluster
Practical workability of AB prescribing guidelines	Guidelines
Practitioner access to AB prescribing guidelines	Guidelines
Practitioner receptiveness to guidelines for prudent AB use	Guidelines
Quality of guideline development process	Guidelines
Quality of hospital AB prescribing guidelines (coherence, evidence-based, up to date)	Guidelines
Quality of national AB prescribing guidelines	Guidelines
Visibility of AB prescribing guidelines	Guidelines
AB effect as growth promotor	Livestock Business Model
Ability to capture value from waste streams	Livestock Business Model
Animal health and welfare	Livestock Business Model
Attractiveness to feed companies to produce medicated feed	Livestock Business Model
Consumers' willingness to pay premium for AB free food	Livestock Business Model
Cost of AB	Livestock Business Model
Ease of application of AB	Livestock Business Model
Environmental impacts	Livestock Business Model
Farmer's perception of impact of biosecurity measures	Livestock Business Model
Heterogeneity of livestock population	Livestock Business Model
Intensity of livestock production	Livestock Business Model
Intensity of global competition	Livestock Business Model
Investments in infrastructure	Livestock Business Model
Investments needed to dose animal feed with AB	Livestock Business Model
Margins per unit of livestock	Livestock Business Model
Pressure of retailers to reduce AB use	Livestock Business Model
Quality of stockmanship	Livestock Business Model
'Generification' of AB market	Market
Attractiveness of reimbursement model	Market



Concept	Cluster
Availability of novel antibiotics	Market
Degree to which reimbursement criteria take into account AB resistance	Market
Incentives to pharma to invest in AB development	Market
Incentives to pharma to keep AB available	Market
Maturity of development model	Market
Pharma company margins on ABs	Market
Pressure on governments to save on medical reimbursement	Market
Product market share of pharma company	Market
Relative supply cost of ABs	Market
Ability to organisationally operationalise One Health concept	Policy
Ability to unambiguously determine consumption levels	Policy
Ability to flexibly allocate funding to interventions	Policy
Ability to rely on international best practices	Policy
Access to an integrated set of indicators	Policy
Available expertise for intersectoral coordination	Policy
Bi-lingual skills of experts and professionals	Policy
Breadth of AB-targeted initiatives	Policy
Centralisation of epidemiological data	Policy
Complexity of host public service FOD VVVL – SPF SPSCAE	Policy
Complexity of Belgian political landscape	Policy
Complexity of national AB institutional landscape	Policy
Continuity of AB policy	Policy
Effectiveness of BAPCOC secretariat	Policy
Funding of intersectoral coordination	Policy
Persistence and continuity of intersectoral coordination	Policy
Pertinence of surveillance and consumption data	Policy
Possibility to assess the reach of information diffusion	Policy



Concept	Cluster
Proliferation of AB-oriented initiatives	Policy
Sense of urgency	Policy
Support from senior public servant	Policy
Transparency of intersectoral coordination governance	Policy
Visibility of BAPCOC	Policy
Ability of hospital management to influence MD prescribing	Stewardship Teams
Access to lab results	Stewardship Teams
Access to relevant interuniversity AB training	Stewardship Teams
Approval of Infectiology and med. microbiology as medical specialty	Stewardship Teams
Assertiveness of infectiologist/ microbiologist	Stewardship Teams
Audit and control of AB stewardship	Stewardship Teams
Authority of AB stewardship teams	Stewardship Teams
Coherence of PPS audits	Stewardship Teams
Collaboration between ABSt teams and Hospital Hygiene Teams	Stewardship Teams
Coupling of hospital financing to AB prescribing-related quality indicators	Stewardship Teams
Degree of details of PPS feedback	Stewardship Teams
Expertise of AB stewardship team members	Stewardship Teams
Funding of in-hospital AB stewardship teams	Stewardship Teams
Level of in-house IT support	Stewardship Teams
Political leverage over allocation of ABS team funding	Stewardship Teams
Receptiveness of ABStT to quality control	Stewardship Teams
Receptiveness of clinicians to direct interference by infectiologist	Stewardship Teams
Reliability and timeliness of individual hospital prescription data	Stewardship Teams
Reliability and timeliness of interhospital benchmarking	Stewardship Teams
Support from hospital management	Stewardship Teams
Support of BAPCOC working group	Stewardship Teams



Concept	Cluster
Workload of in-hospital AB stewardship teams	Stewardship Teams
Ability of AMCRA to federate relevant actors	Vet sector autoregulation
Access to funding for scientific and admin coordination	Vet sector autoregulation
Consistency of messaging	Vet sector autoregulation
Effectiveness of sectorial benchmark	Vet sector autoregulation
Farmers organisations' support for AB policy	Vet sector autoregulation
Financial compensation for admin impact of monitoring	Vet sector autoregulation
Granularity of consumption data	Vet sector autoregulation
Incentives from AB producers	Vet sector autoregulation
Strength of international AB regulation regimes	Vet sector autoregulation
Visibility of AMCRA	Vet sector autoregulation
Visibility of prevention campaigns	Vet sector autoregulation
Effectiveness of AB registration system	Vet sector regulation
Reliability of tests	Vet sector regulation
Stringency of controls	Vet sector regulation
Use of analytical diagnostic tools	Vet sector regulation
Variety in production models	Vet sector regulation
Assertiveness of farmer's demand for AB	Veterinarians
Coherence between guidelines	Veterinarians
Independence of analytic labs	Veterinarians
Likelihood of AB prescription by other vet	Veterinarians
Prescription of AB for companion animals	Veterinarians
Preventative animal consumption of medicated animal feed	Veterinarians
Reliability of antibiogram testing	Veterinarians
Role and authority of vet in production model	Veterinarians
Strength of veterinarian independence in relation to pet owner	Veterinarians
Veterinarian awareness of AMR	Veterinarians



Concept	Cluster
Veterinary treatment compliance	Veterinarians
Willingness of farmer to pay for counselling	Veterinarians

ABSt: Antibiotic Stewardship; ABStT: Antibiotic Stewardship Teams; AMCRA: Belgian Centre of Expertise on Antimicrobial Consumption and Resistance in Animals; AP: Ambulatory Practitioner; BAPCOC: Belgian Antibiotic Policy Coordination Committee; LOK - GLEM: Lokale kwaliteitsgroep -Groupe local d'évaluation médicale; MD: Medical Doctor; FOD VVVL – SPF SPSCAE: Federal Public Service Health, Food Chain Safety and Environment ('Federale overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu'/'Service public fédéral Santé publique, Sécurité de la Chaîne Alimentaire et Environnement'); PPS: Point prevalence survey.

Appendix 5.2. Connections between concepts

Table 57 lists all the connections between concepts in the systems map, ordered alphabetically.

Table 57 – Connections between concepts in the systems map

Tail concept	Head concept	Type of connection
AB auto- medication	Appropriateness of Animal AB consumption	red
AB as convenient, accepted reinforcement of expert status	Prudence of AB prescription for humans	red
AB as convenient, accepted reinforcement of expert status	Weight of high volume prescription culture	blue
AB effect as growth promotor	Pressure on profitability	red
AB effect as growth promotor	Willingness of feed companies to support AB auto-regulation	blue
AB prescription for pets by APs	Prescription of AB for companion animals	blue
AB treatment withdrawal time	Farmers' receptiveness to guidelines for prudent AB use	red
AB treatment withdrawal time	Pressure on profitability	blue
Ability to adjust packaging size to treatment	AB auto- medication	red
Ability to adjust packaging size to treatment	Appropriateness of Animal AB consumption	blue
Ability to adjust packaging size to treatment	Patient AB Auto-medication	red
Ability to frame positive, empowering messages	Effectiveness of sensitisation campaigns	blue
Ability of AMCRA to federate relevant actors	Effectiveness of sector's autoregulation	blue
Ability of hospital management to influence MD prescribing	Effectiveness of AB stewardship teams in hospitals	blue
Ability to impose restrictions on 'empirical prescription'	Prudence of AB prescription for humans	blue



Tail concept	Head concept	Type of connection
Ability to organisationally operationalise One Health concept	Effectiveness of AB policy	blue
Ability to unambiguously determine consumption levels	Coherence of AB policy	blue
Ability to capture value from waste streams	Pressure on profitability	red
Ability to flexibly allocate funding to interventions	Effectiveness of AB policy	blue
Ability to flexibly allocate funding to interventions	Effectiveness of intersectoral coordination	blue
Ability to reach citizens at an early age	Effectiveness of sensitisation campaigns	blue
Ability to reach indifferent segment of target audience	Effectiveness of sensitisation campaigns	blue
Ability to rely on international best practices	Effectiveness of AB policy	blue
AB prescribing-related economic interest of veterinarians	Effectiveness of sector's autoregulation	red
AB prescribing-related economic interest of veterinarians	Prudence of veterinary AB prescription	red
AB prescribing-related economic interest of veterinarians	Strength of historical recommendations for use of AB	blue
AB prescribing-related economic interest of veterinarians	Vet's receptiveness to AB prescribing guidelines	red
Access to lab results	Effectiveness of AB stewardship teams in hospitals	blue
Access to lab results	Use of appropriate AB	blue
Access to AB prescribing guidelines	Farmers' receptiveness to guidelines for prudent AB use	blue
Access to AB prescribing guidelines	Prudence of veterinary AB prescription	blue
Access to AB prescribing guidelines	Vet's receptiveness to AB prescribing guidelines	blue
Access to an integrated set of indicators	Coherence of AB policy	blue
Access to antibiotic use counselling	Farmers' receptiveness to guidelines for prudent AB use	blue
Access to funding for scientific and admin coordination	Effectiveness of sector's autoregulation	blue
Access to hospital-led infection prevention networks	Practitioner expertise regarding prudent AB use	blue
Access to nationwide media	Effectiveness of sensitisation campaigns	blue
Access to patient medication history	Propensity of APs to avoid short-term patient risk	red
Access to patient medication history	Prudence of AB prescription for humans	blue
Access to relevant interuniversity AB training	Expertise of AB stewardship team members	blue
Access to specialised expertise to design sensitisation campaigns	Ability to frame positive, empowering messages	blue



Tail concept	Head concept	Type of connection
Access to specialised expertise to design sensitisation campaigns	Ability to reach citizens at an early age	blue
Access to specialised expertise to design sensitisation campaigns	Ability to reach indifferent segment of target audience	blue
Access to trusted sources of scientific expertise	Practitioner expertise regarding prudent AB use	blue
Access to and correct use of rapid diagnostic aids	Prudence of AB prescription for humans	blue
Accessibility and visibility of BAPCOC website	Practitioner access to AB prescribing guidelines	red
Age of AP	Readiness of APs to question AB prescribing behaviour	red
Animal health and welfare	Appropriateness of Animal AB consumption	red
Animal health and welfare	Risk of disease	red
Antimicrobial resistance	Appropriateness of Animal AB consumption	red
Antimicrobial resistance	Impact of resistant pathogens on farmer's health and business	blue
AP understanding of detrimental effects on individuals and populations of long-term AB use	Prudence of AB prescription for humans	blue
AP ability to communicate with patients on AB effects	Assumed patient demand for AB	red
AP ability to communicate with patients on AB effects	Patient uncertainty about health outcomes	red
AP ability to communicate with patients on AB effects	Patient understanding of effects of AB use	blue
Appropriateness of Animal AB consumption	Animal health and welfare	blue
Appropriateness of Animal AB consumption	Antimicrobial resistance	red
Appropriateness of Animal AB consumption	Presence of AB in the environment	blue
Appropriateness of human AB Consumption	Antimicrobial resistance	red
Appropriateness of human AB Consumption	Volume of AB in waste water streams	blue
Approval of Infectiology and med. microbiology as medical specialty	Assertiveness of infectiologist/ microbiologist	blue
Approval of Infectiology and med. microbiology as medical specialty	Effectiveness of AB stewardship teams in hospitals	blue
Approval of Infectiology and med. microbiology as medical specialty	Fragmentation of infectiology teaching base	red
(Assertiveness of) Patient demand for ABs	Prudence of AB prescription for humans	red
(Assertiveness of) Patient demand for ABs	Strength of AP independence in relation to patient	red
Assertiveness of farmer's demand for AB	Prudence of veterinary AB prescription	red



Tail concept	Head concept	Type of connection
Assertiveness of farmer's demand for AB	Role and authority of vet in production model	grey
Assertiveness of infectiologist/ microbiologist	Receptiveness of clinicians to direct interference by infectiologist	blue
Assumed patient demand for AB	Strength of AP independence in relation to patient	red
Attractiveness of quality labels	Farmers' receptiveness to guidelines for prudent AB use	blue
Attractiveness of reimbursement model	Incentives to pharma to invest in AB development	blue
Attractiveness of reimbursement model	Incentives to pharma to keep AB available	blue
Attractiveness to feed companies to produce medicated feed	Willingness of feed companies to support AB auto-regulation	blue
Audit and control of AB stewardship	Effectiveness of AB stewardship teams in hospitals	blue
Audit and control of AB stewardship	Effectiveness of implementation of AB prescribing guidelines	blue
Audit and control of AB stewardship	Receptiveness of ABStT to quality control	blue
Authority of AB stewardship teams	Effectiveness of AB stewardship teams in hospitals	blue
Availability of old ABs	Use of appropriate AB	blue
Availability of benchmarking	Appropriateness of Animal AB consumption	blue
Availability of benchmarking	Farmers' receptiveness to guidelines for prudent AB use	blue
Availability of cost-efficient profitable alternative treatments	Animal health and welfare	blue
Availability of cost-efficient profitable alternative treatments	Antimicrobial resistance	red
Availability of cost-efficient profitable alternative treatments	Appropriateness of Animal AB consumption	blue
Availability of cost-efficient profitable alternative treatments	Environmental impacts	blue
Availability of cost-efficient profitable alternative treatments	Farmers' receptiveness to guidelines for prudent AB use	blue
Availability of cost-efficient profitable alternative treatments	Pressure on profitability	blue
Availability of novel antibiotics	Use of appropriate AB	grey
Availability of tailored epidemiological data	Practitioner expertise regarding prudent AB use	blue
Available expertise for intersectoral coordination	Effectiveness of AB policy	blue
Bi-lingual skills of experts and professionals	Effectiveness of intersectoral coordination	blue
Breadth of AB-targeted initiatives	Effectiveness of AB policy	blue
Centralisation of epidemiological data	Access to an integrated set of indicators	blue



Tail concept	Head concept	Type of connection
Clinical interest of AB to medical practitioners	Practitioner expertise regarding prudent AB use	blue
Clinical interest of AB to medical practitioners	Practitioner receptiveness to guidelines for prudent AB use	blue
Coherence amongst national guidelines	Effectiveness of implementation of AB prescribing guidelines	blue
Coherence between guidelines	Vet's receptiveness to AB prescribing guidelines	blue
Coherence between national and internal guidelines	Effectiveness of implementation of AB prescribing guidelines	blue
Coherence of AB policy	Effectiveness of AB policy	blue
Coherence of AB policy	Reliability and timeliness of interhospital benchmarking	blue
Coherence of PPS audits	Effectiveness of AB stewardship teams in hospitals	blue
Coherence of PPS audits	Workload of in-hospital AB stewardship teams	red
Collaboration between ABSt teams and Hospital Hygiene Teams	Effectiveness of AB stewardship teams in hospitals	blue
Complexity of host public service FOD VVVL – SPF SPSCAE	Available expertise for intersectoral coordination	red
Complexity of host public service FOD VVVL – SPF SPSCAE	Effectiveness of intersectoral coordination	red
Complexity of host public service FOD VVVL – SPF SPSCAE	Funding of intersectoral coordination	red
Complexity of Belgian political landscape	Effectiveness of intersectoral coordination	red
Complexity of national AB institutional landscape	Coherence of AB policy	red
Complexity of national AB institutional landscape	Effectiveness of AB policy	blue
Consistency of messaging	Effectiveness of sector's autoregulation	blue
Consumers' willingness to pay premium for AB free food	Pressure of retailers to reduce AB use	blue
Consumers' willingness to pay premium for AB free food	Pressure on profitability	red
Continuity of AB policy	Effectiveness of AB policy	blue
Cost of AB	Appropriateness of Animal AB consumption	red
Cost of AB	Pressure on profitability	red
Cost to patient of antibiotics	(Assertiveness of) Patient demand for ABs	blue
Coupling of hospital financing to AB prescribing-related quality indicators	Effectiveness of AB stewardship teams in hospitals	blue
Coupling of hospital financing to AB prescribing-related quality indicators	Political leverage over allocation of ABSt team funding	blue
Coupling of hospital financing to AB prescribing-related quality indicators	Practitioner receptiveness to guidelines for prudent AB use	blue



Tail concept	Head concept	Type of connection
Cross- fertilisation between human and veterinary expertise	Practitioner expertise regarding prudent AB use	blue
Cross- therapeutic integration of AB guidelines	Effectiveness of implementation of AB prescribing guidelines	blue
Cultural sensitivity of campaigns	Effectiveness of sensitisation campaigns	blue
Degree of details of PPS feedback	Effectiveness of AB stewardship teams in hospitals	blue
Degree to which livelihood depends on farming	Farmers' receptiveness to guidelines for prudent AB use	
Degree to which patients trust their medicines rather than own healing resources	(Assertiveness of) Patient demand for ABs	blue
Degree to which reimbursement criteria take into account AB resistance	Attractiveness of reimbursement model	blue
Ease of application of AB	Appropriateness of Animal AB consumption	red
Ease of application of AB	Pressure on profitability	red
Effectiveness of BAPCOC secretariat	Effectiveness of intersectoral coordination	blue
Effectiveness of AB policy	Prudence of AB prescription for humans	blue
Effectiveness of sector's autoregulation	Prudence of veterinary AB prescription	blue
Effectiveness of sensitisation campaigns	Effectiveness of AB policy	blue
Effectiveness of AB registration system	Enforceability of regulation of vet AB use	blue
Effectiveness of AB stewardship teams in hospitals	Practitioner access to AB prescribing guidelines	blue
Effectiveness of AB stewardship teams in hospitals	Practitioner receptiveness to guidelines for prudent AB use	blue
Effectiveness of AB stewardship teams in hospitals	Quality of guideline development process	blue
Effectiveness of implementation of AB prescribing guidelines	Practitioner receptiveness to guidelines for prudent AB use	blue
Effectiveness of intersectoral coordination	Available expertise for intersectoral coordination	blue
Effectiveness of intersectoral coordination	Effectiveness of AB policy	blue
Effectiveness of pharmacies as communication gateways	Effectiveness of sensitisation campaigns	blue
Effectiveness of sectorial benchmark	Effectiveness of sector's autoregulation	blue
Effectiveness of sectorial benchmark	Vet's receptiveness to AB prescribing guidelines	blue
Emergency visits in ambulatory and hospital car	Propensity of APs to avoid short-term patient risk	blue
Emergency visits in ambulatory and hospital car	Prudence of AB prescription for humans	red



Tail concept	Head concept	Type of connection
Emotional loading of patient framing of common complaints	(Assertiveness of) Patient demand for ABs	blue
Enforceability of regulation of vet AB use	Appropriateness of Animal AB consumption	blue
Enforceability of regulation of vet AB use	Effectiveness of sector's autoregulation	blue
Enforceability of regulation of vet AB use	Farmers' receptiveness to guidelines for prudent AB use	blue
Enforceability of regulation of vet AB use	Prudence of veterinary AB prescription	blue
Expertise of AB stewardship team members	Effectiveness of AB stewardship teams in hospitals	blue
Expertise/ basic education of medical practitioners (MPs)	Effectiveness of AB stewardship teams in hospitals	blue
Extent of human migratory flows	Antimicrobial resistance	blue
Farmer autonomy in production model	Farmers' receptiveness to guidelines for prudent AB use	grey
Farmer's perception of impact of biosecurity measures	Quality of stockmanship	blue
Farmers organisations' support for AB policy	Effectiveness of sector's autoregulation	blue
Farmers' knowledge of AB pharmacology	Farmers' receptiveness to guidelines for prudent AB use	blue
Farmers' receptiveness to guidelines for prudent AB use	Appropriateness of Animal AB consumption	blue
Farmers' receptiveness to guidelines for prudent AB use	Assertiveness of farmer's demand for AB	red
Farmers' receptiveness to guidelines for prudent AB use	Effectiveness of sector's autoregulation	blue
Fatigue due to AB sensitisation messages	Effectiveness of sensitisation campaigns	red
Financial compensation for admin impact of monitoring	Effectiveness of sector's autoregulation	blue
Financial incentives based on benchmarking of prescription behaviour	Practitioner receptiveness to guidelines for prudent AB use	blue
Financial incentives to APs to reduce AB prescription	Readiness of APs to question AB prescribing behaviour	blue
Fragmentation of infectiology teaching base	Quality of academic training on prudent AB prescription	blue
Frequency of consultation	Prudence of AB prescription for humans	red
Funding of in-hospital AB stewardship teams	Effectiveness of AB stewardship teams in hospitals	blue
Funding of in-hospital AB stewardship teams	Quality of national AB prescribing guidelines	blue
Funding for guideline development	Quality of national AB prescribing guidelines	blue
Funding of campaigns	Effectiveness of sensitisation campaigns	blue
Funding of intersectoral coordination	Access to specialised expertise to design sensitisation campaigns	blue



Tail concept	Head concept	Type of connection
Funding of intersectoral coordination	Available expertise for intersectoral coordination	blue
Funding of intersectoral coordination	Effectiveness of intersectoral coordination	blue
Funding of intersectoral coordination	Persistence and continuity of intersectoral coordination	blue
'Generification' of AB market	Availability of novel antibiotics	red
'Generification' of AB market	Incentives to pharma to invest in AB development	red
'Generification' of AB market	Pharma company margins on ABs	red
'Generification' of AB market	Price of ABs	red
'Generification' of AB market	Product market share of pharma company	red
Government support for prudent AB use	Effectiveness of sector's autoregulation	blue
Government support for prudent AB use	Farmers' receptiveness to guidelines for prudent AB use	blue
Granularity of consumption data	Effectiveness of sector's autoregulation	blue
Handover between hospital and AP	Prudence of AB prescription for humans	blue
Heterogeneity of livestock population	Risk of disease	blue
Impact of resistant pathogens on farmer's health and business	Farmers' receptiveness to guidelines for prudent AB use	blue
Impact of fee for service reimbursement	Prudence of AB prescription for humans	red
Incentives associated to individual prescription profiles	Practitioner expertise regarding prudent AB use	blue
Incentives associated to individual prescription profiles	Readiness of APs to question AB prescribing behaviour	blue
Incentives from AB producers	AB prescribing-related economic interest of veterinarians	blue
Incentives from AB producers	Effectiveness of sector's autoregulation	red
Incentives from AB producers	Strength of historical recommendations for use of AB	blue
Incentives to pharma to invest in AB development	Availability of novel antibiotics	blue
Incentives to pharma to keep AB available	Availability of old ABs	blue
Incentives via accreditation for 'life long learning'	Practitioner expertise regarding prudent AB use	blue
Independence of analytic labs	Prudence of veterinary AB prescription	blue
Independence from industry funding	Quality of national AB prescribing guidelines	blue
Influence of AB prescription behaviour of senior peers	Weight of high volume prescription culture	blue



Tail concept	Head concept	Type of connection
Information overload of medical practitioners (MPs)	Effectiveness of sensitisation campaigns	red
Information overload of medical practitioners (MPs)	Practitioner receptiveness to guidelines for prudent AB use	red
Information overload of medical practitioners (MPs)	Readiness of APs to question AB prescribing behaviour	red
Intensity of livestock production	Effectiveness of sector's autoregulation	blue
Intensity of livestock production	Environmental impacts	blue
Intensity of livestock production	Risk of disease	blue
Intensity of global competition	Margins per unit of livestock	red
International coherence of AB guidelines	Perceived legitimacy of AB prescribing guidelines	blue
International consensus on list of critically important ABs	Perceived legitimacy of AB prescribing guidelines	blue
Investments in infrastructure	Animal health and welfare	blue
Investments in infrastructure	Pressure on profitability	blue
Investments needed to dose animal feed with AB	Attractiveness to feed companies to produce medicated feed	red
Involvement of pharma sector in guideline development	Perceived legitimacy of AB prescribing guidelines	blue
Level of farmer's education	Farmers' receptiveness to guidelines for prudent AB use	blue
Level of farmer's education	Quality of stockmanship	blue
Level of in-house IT support	Effectiveness of AB stewardship teams in hospitals	blue
Likelihood of AB prescription by other vet	Prudence of veterinary AB prescription	red
Likelihood of AB prescription by other APs	Prudence of AB prescription for humans	red
Likelihood of continuation of farm	Farmers' receptiveness to guidelines for prudent AB use	red
Likelihood of continuation of farm	Investments in infrastructure	blue
Margins per unit of livestock	Intensity of livestock production	blue
Margins per unit of livestock	Pressure on profitability	red
Maturity of development model	Availability of novel antibiotics	red
Obligation of MD certificate for one-day sick leave	Frequency of consultation	blue
Patient knowledge of common complaints	(Assertiveness of) Patient demand for ABs	red
Patient knowledge of common complaints	Weight of AB consumption culture	red



Tail concept	Head concept	Type of connection
Patient out-of-pocket expense per consultation	(Assertiveness of) Patient demand for ABs	blue
Patient treatment compliance	Appropriateness of human AB Consumption	blue
Patient uncertainty about health outcomes	(Assertiveness of) Patient demand for ABs	blue
Patient understanding of effects of AB use	(Assertiveness of) Patient demand for ABs	red
Patient understanding of effects of AB use	Patient treatment compliance	blue
Patient understanding of effects of AB use	Patient uncertainty about health outcomes	red
Patient understanding of effects of AB use	Patient AB Auto-medication	red
Patient AB Auto-medication	Appropriateness of human AB Consumption	red
Perceived legitimacy of AB prescribing guidelines	Effectiveness of sector's autoregulation	blue
Perceived legitimacy of AB prescribing guidelines	Vet's receptiveness to AB prescribing guidelines	blue
Persistence and continuity of intersectoral coordination	Effectiveness of AB policy	blue
Persistence and continuity of intersectoral coordination	Effectiveness of intersectoral coordination	blue
Persistence of sensitisation campaigns	Effectiveness of sensitisation campaigns	blue
Persistence of sensitisation campaigns	Fatigue due to AB sensitisation messages	blue
Personal character of relationship between patient and AP	Strength of AP independence in relation to patient	blue
Pertinence of surveillance and consumption data	Coherence of AB policy	blue
Pharma company margins on ABs	Availability of old ABs	red
Political leverage over allocation of ABSt team funding	Effectiveness of AB stewardship teams in hospitals	blue
Political leverage over allocation of ABSt team funding	Support from hospital management	blue
Possibility of pharma co to contribute to guideline development	Quality of guideline development process	blue
Possibility of practitioners to contribute to guideline development	Effectiveness of implementation of AB prescribing guidelines	blue
Possibility of practitioners to contribute to guideline development	Practitioner receptiveness to guidelines for prudent AB use	blue
Possibility of practitioners to contribute to guideline development	Quality of guideline development process	blue
Possibility to assess the reach of information diffusion	Effectiveness of AB policy	blue
Possibility to have personalised, authoritative feedback on AP AB PRESCRIBING behaviour	Influence of AB prescription behaviour of senior peers	red



Tail concept	Head concept	Type of connection
Possibility to have personalised, authoritative feedback on AP AB PRESCRIBING behaviour	Practitioner expertise regarding prudent AB use	blue
Possibility to have personalised, authoritative feedback on AP AB PRESCRIBING behaviour	Readiness of APs to question AB prescribing behaviour	blue
Possibility to receive feedback and discuss best practices with peers (incl. through LOKs - GLEMs)	Practitioner expertise regarding prudent AB use	blue
Practical workability of AB prescribing guidelines	Effectiveness of implementation of AB prescribing guidelines	blue
Practitioner acceptance of formal audits	Readiness of APs to question AB prescribing behaviour	blue
Practitioner access to AB prescribing guidelines	Effectiveness of implementation of AB prescribing guidelines	blue
Practitioner access to AB prescribing guidelines	Practitioner receptiveness to guidelines for prudent AB use	blue
Practitioner authority as perceived by patients	Strength of AP independence in relation to patient	blue
Practitioner expertise regarding prudent AB use	AP understanding of detrimental effects on individuals and populations of long-term AB use	blue
Practitioner expertise regarding prudent AB use	Prudence of AB prescription for humans	blue
Practitioner expertise regarding prudent AB use	Self-confidence of AP	blue
Practitioner identification with expert status (ego)	Prudence of AB prescription for humans	red
Practitioner identification with expert status (ego)	Readiness of APs to question AB prescribing behaviour	red
Practitioner receptiveness to guidelines for prudent AB use	Effectiveness of AB policy	blue
Practitioner receptiveness to guidelines for prudent AB use	Effectiveness of implementation of AB prescribing guidelines	blue
Practitioner receptiveness to guidelines for prudent AB use	Practitioner expertise regarding prudent AB use	blue
Practitioner receptiveness to guidelines for prudent AB use	Prudence of AB prescription for humans	blue
Practitioners' insistence on therapeutic freedom	Ability to impose restrictions on 'empirical prescription'	red
Practitioners' insistence on therapeutic freedom	Practitioner receptiveness to guidelines for prudent AB use	red
Prescription incentives from AB producers	Quality and availability of information through LOKs - GLEMs (APs)	red
Prescription incentives from AB producers	Use of appropriate AB	red
Prescription incentives from AB producers	Weight of high volume prescription culture	blue
Prescription of AB for companion animals	Presence of AB in the environment	blue



Tail concept	Head concept	Type of connection
Presence of AB in the environment	Antimicrobial resistance	blue
Pressure on citizens to perform	(Assertiveness of) Patient demand for ABs	blue
Pressure of retailers to reduce AB use	Farmers' receptiveness to guidelines for prudent AB use	blue
Pressure on profitability	Assertiveness of farmer's demand for AB	blue
Pressure on profitability	Farmers' receptiveness to guidelines for prudent AB use	red
Pressure on governments to save on medical reimbursement	'Generification' of AB market	blue
Pressure on governments to save on medical reimbursement	Attractiveness of reimbursement model	red
Pressure on governments to save on medical reimbursement	Price of ABs	red
Preventative animal consumption of medicated animal feed	Appropriateness of Animal AB consumption	red
Preventative animal consumption of medicated animal feed	Risk of disease	red
Price of ABs	Pharma company margins on ABs	blue
Price of ABs	Weight of high volume prescription culture	blue
Product market share of pharma company	Availability of old ABs	blue
Product market share of pharma company	Relative supply cost of ABs	red
Proliferation of AB-oriented initiatives	Coherence of AB policy	red
Propensity of APs to avoid short-term patient risk	Prudence of AB prescription for humans	red
Prudence of AB prescription for humans	(Assertiveness of) Patient demand for ABs	red
Prudence of AB prescription for humans	Appropriateness of human AB Consumption	blue
Prudence of veterinary AB prescription	Appropriateness of Animal AB consumption	blue
Prudence of veterinary AB prescription	Preventative animal consumption of medicated animal feed	red
Quality and availability of information through LOKs - GLEMs (APs)	Practitioner expertise regarding prudent AB use	blue
Quality of academic training on prudent AB prescription	Expertise/ basic education of medical practitioners (MPs)	blue
Quality of academic training on prudent AB prescription	Practitioner expertise regarding prudent AB use	blue
Quality of academic training on prudent AB prescription	Quality and availability of information through LOKs - GLEMs (APs)	blue
Quality of guideline development process	Effectiveness of implementation of AB prescribing guidelines	blue



Tail concept	Head concept	Type of connection
Quality of hospital AB prescribing guidelines (coherence, evidence-based, up to date)	Effectiveness of implementation of AB prescribing guidelines	blue
Quality of impact assessments of campaigns	Effectiveness of sensitisation campaigns	blue
Quality of national AB prescribing guidelines	Effectiveness of implementation of AB prescribing guidelines	blue
Quality of stockmanship	Animal health and welfare	blue
Quality of stockmanship	Farmer's perception of impact of biosecurity measures	blue
Quality of stockmanship	Investments in infrastructure	blue
Readiness of APs to question AB prescribing behaviour	Prudence of AB prescription for humans	blue
Receptiveness of ABStT to quality control	Effectiveness of AB stewardship teams in hospitals	blue
Receptiveness of clinicians to direct interference by infectiologist	Effectiveness of AB stewardship teams in hospitals	blue
Relative supply cost of ABs	Availability of old ABs	red
Reliability and timeliness of individual hospital prescription data	Effectiveness of AB stewardship teams in hospitals	blue
Reliability of tests	Enforceability of regulation of vet AB use	blue
Reliability and timeliness of interhospital benchmarking	Effectiveness of AB stewardship teams in hospitals	blue
Reliability of antibiogram testing	Prudence of veterinary AB prescription	blue
Risk of disease	Appropriateness of Animal AB consumption	red
Risk of disease	Farmers' receptiveness to guidelines for prudent AB use	red
Risk of disease	Pressure on profitability	blue
Role and authority of vet in production model	AB auto- medication	red
Role and authority of vet in production model	Farmers' receptiveness to guidelines for prudent AB use	blue
Role and authority of vet in production model	Prudence of veterinary AB prescription	blue
Role and authority of vet in production model	Vet's receptiveness to AB prescribing guidelines	blue
Safety and effectiveness of 3d and 4th gen. ABs	Farmers' receptiveness to guidelines for prudent AB use	red
Self-confidence of AP	Strength of AP independence in relation to patient	blue
Sense of responsibility of parents towards children	(Assertiveness of) Patient demand for ABs	blue
Sense of urgency	Effectiveness of AB policy	blue



Tail concept	Head concept	Type of connection
Sense of urgency	Support from senior public servant	blue
Strength of historical recommendations for use of AB	Effectiveness of sector's autoregulation	red
Strength of historical recommendations for use of AB	Farmers' receptiveness to guidelines for prudent AB use	red
Strength of international AB regulation regimes	Farmers organisations' support for AB policy	blue
Strength of veterinarian independence in relation to pet owner	Prudence of veterinary AB prescription	blue
Strength of AP independence in relation to patient	(Assertiveness of) Patient demand for ABs	red
Strength of AP independence in relation to patient	AB prescription for pets by APs	red
Strength of AP independence in relation to patient	Prudence of AB prescription for humans	blue
Stringency of controls	Enforceability of regulation of vet AB use	blue
Stringency of controls	Prudence of veterinary AB prescription	blue
Support from hospital management	Authority of AB stewardship teams	blue
Support from senior public servant	Continuity of AB policy	blue
Support from senior public servant	Effectiveness of AB policy	blue
Support from senior public servant	Effectiveness of intersectoral coordination	blue
Support from senior public servant	Effectiveness of intersectoral coordination	
Support of BAPCOC working group	Access to relevant interuniversity AB training	blue
Support of BAPCOC working group	Effectiveness of AB stewardship teams in hospitals	blue
Time available for consultation	Patient understanding of effects of AB use	blue
Time available for consultation	Strength of AP independence in relation to patient	blue
Timeliness of sensitisation campaigns	Effectiveness of sensitisation campaigns	blue
Transparency of intersectoral coordination governance	Effectiveness of AB policy	blue
Use of analytical diagnostic tools	Enforceability of regulation of vet AB use	blue
Use of appropriate AB	Prudence of AB prescription for humans	blue
Use of electronic prescription system to collect AB prescribing data, incl. diagnosis	Possibility to have personalised, authoritative feedback on AP AB PRESCRIBING behaviour	blue
Use of electronic prescription system to collect AB prescribing data, incl. diagnosis	Readiness of APs to question AB prescribing behaviour	blue



Tail concept	Head concept	Type of connection
Variety in production models	Enforceability of regulation of vet AB use	blue
Vet's receptiveness to AB prescribing guidelines	Attractiveness to feed companies to produce medicated feed	red
Vet's receptiveness to AB prescribing guidelines	Prudence of veterinary AB prescription	blue
Vet's receptiveness to AB prescribing guidelines	Role and authority of vet in production model	blue
Veterinarian awareness of AMR	Vet's receptiveness to AB prescribing guidelines	blue
Veterinarians' communication skills	Farmers' receptiveness to guidelines for prudent AB use	blue
Veterinary treatment compliance	Antimicrobial resistance	red
Veterinary treatment compliance	Prudence of veterinary AB prescription	blue
Visibility of AB prescribing guidelines	Access to AB prescribing guidelines	blue
Visibility of AMCRA	Effectiveness of sector's autoregulation	blue
Visibility of BAPCOC	Effectiveness of intersectoral coordination	blue
Visibility of prevention campaigns	Effectiveness of sector's autoregulation	blue
Volume of AB in waste water streams	Presence of AB in the environment	blue
Weight of AB consumption culture	(Assertiveness of) Patient demand for ABs	blue
Weight of high volume prescription culture	Effectiveness of AB policy	red
Weight of high volume prescription culture	Prudence of AB prescription for humans	red
Weight of high volume prescription culture	Readiness of APs to question AB prescribing behaviour	red
Willingness of feed companies to support AB auto-regulation	Effectiveness of sector's autoregulation	blue
Willingness of feed companies to support AB auto-regulation	Preventative animal consumption of medicated animal feed	red
Willingness of feed companies to support AB auto-regulation	Vet's receptiveness to AB prescribing guidelines	blue
Willingness of farmer to pay for counselling	AB prescribing-related economic interest of veterinarians	red
Workload of in-hospital AB stewardship teams	Effectiveness of AB stewardship teams in hospitals	red
Years of practice	Practitioner expertise regarding prudent AB use	red

ABSt: Antibiotic Stewardship; ABStT: Antibiotic Stewardship Teams; AMCRA: Belgian Centre of Expertise on Antimicrobial Consumption and Resistance in Animals; AP: Ambulatory Practitioner; BAPCOC: Belgian Antibiotic Policy Coordination Committee; LOK - GLEM: Lokale kwaliteitsgroep -Groupe local d'évaluation médicale; MD: Medical Doctor; FOD VVVL – SPF SPSCAE: Federal Public Service Health, Food Chain Safety and Environment ('Federale overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu'/Service public fédéral Santé publique, Sécurité de la Chaîne Alimentaire et Environnement'); PPS: Point prevalence survey.



Appendix 5.3. Assessment of the scope of the systems map

Table 58 – Determinants of human antibiotic use identified in the literature and related concepts in the systems map

Determinant identified in the literature	Related concepts in the systems map
RELATED TO PRESCRIBERS	
Age/years of practice	Age of AP, Years of practice
Gender	-
Place of residence/practice	-
Professional training	Quality of academic training on prudent antibiotic prescription
Uncertainty and fear related to diagnosis and outcome	Propensity of ambulatory practitioners to avoid short term patient risk
Chagrin factor or “better safe than sorry”	Propensity of ambulatory practitioners to avoid short term patient risk. Likelihood of antibiotic prescription by other ambulatory practitioners
Perception of patient demand	Assertiveness of patient demand for antibiotics; Strength of ambulatory practitioner independence in relation to patient
Disease labelling by GP	-
Time per patient	Time available for consultation
Confidence in guidelines	Practitioner receptiveness to guidelines for prudent antibiotic prescription
GP-patient relationship	Strength of ambulatory independence in relation to patient; Ambulatory practitioner to communicate with patients on antibiotic effects
NOT AB resistance	Ambulatory practitioner understanding of detrimental effects on individuals and populations of long-term antibiotic use
RELATED TO HEALTH CARE SYSTEM	
Type of practice	Impact of fee for service (as opposed to lump sum in grouped practices / capitation)
Size of practice	Time available for consultation
Consultation rates	Time available for consultation
Reimbursement for antibiotics	Cost to patient of antibiotics
Financing scheme for consultations	Impact of fee for service reimbursements
Administrative rules	
RELATED TO THE PATIENT	



Determinant identified in the literature	Related concepts in the systems map
Age and gender	-
Place/residence	-
Education	-
Patient knowledge	Patient knowledge of common complaints; Patient understanding of effects of antibiotic use
Patient anxiety	Patient uncertainty about health outcomes
Disease severity and patient vulnerability perceived by physician	Emergency visits in ambulatory and hospital care
Disease perception and labelling by patient	Emotional loading of patient framing of common complaints
Expectations for antibiotics	Patient understanding of effects of antibiotic use; Degree to which patients trust their medicines rather than own healing resources

AB: antibiotic(s); AP: ambulatory practitioner; GP: general practitioner

Table 59 – Determinants of veterinary antibiotic use identified from the literature and related concepts in the systems map

Determinant identified in the literature	Related concepts in the systems map
Agricultural factors (e.g. housing, feeding systems)	Investments in infrastructure
Animal age	-
Animal body weight	-
Animal species and associated behaviour	-
Attitudes of senior and junior veterinarians towards AB use	-
Attitudes, risk perception and aversion	-
Awareness of recommendations for responsible AB use	Access to guidelines; Perceived legitimacy of antibiotic prescription guidelines
Capacity of veterinarian to elicit farmers' true goals beliefs and tailor advices to this knowledge base	-
Client pressure and dependency	Assertiveness of farmer's demand for antibiotics; Strength of veterinarian independence in relation to pet owner; Role and authority of vet in production model
Client pressure and expectations	Assertiveness of farmer's demand for antibiotics; Strength of veterinarian independence in relation to pet owner



Determinant identified in the literature	Related concepts in the systems map
Clinical signs	-
Competition between veterinarians	Likelihood of prescription by other vet
Confidence in own knowledge regarding disease prevention	-
Conflicting advices to farmers	-
Cost of therapy, financial constraints	Cost of antibiotics; Pressure on profitability; Availability of cost-efficient, profitable alternative treatments
Degree of integration ^{ss} and Integration size	Role and authority of vet in production model, farmer autonomy in production model
Diagnostic tests	Reliability of antibiogram testing
Differing views on the indications for prescribing AB	-
Drug availability	-
Drug efficacy	Safety and effectiveness of 3d and 4 th generation antibiotics
Drug sales and veterinary pharmacy	Antibiotic-related economic interest of veterinarians
Duration of AB therapy	-
Effectiveness of AB use written protocols	Visibility of antibiotic prescription guidelines; Access to guidelines; Perceived legitimacy of guidelines
Farmers' past experiences	Impact of resistant pathogens on farmer's health and business
Financial barriers for structural veterinary herd health advisory services	Willingness of farmer to pay for counselling
Financial dependency on clients/farmers	Antibiotic-related economic interest of veterinarians
Formulation and ease of administration	Ease of application of antibiotics
Guidelines and guideline use	Visibility of antibiotic prescription guidelines; Access to guidelines; Perceived legitimacy of guidelines
Health status of the herd	Animal health and welfare
Hierarchical structure and professional relationships	-
Importation of pig products and pressure from retailers	Pressure of retailers to reduce antibiotics use
Influence of staff effectiveness meetings	-



Determinant identified in the literature	Related concepts in the systems map
Knowledge of (non)infectious diseases	-
Lack of farmers' compliance to veterinary recommendations	Veterinary treatment compliance; Antibiotic automedication
Lack of collaboration between advisors	-
Length of consultation	-
Meet clients expectations	Assertiveness of farmer's demand for antibiotics; Strength of veterinarian independence in relation to pet owner; Role and authority of vet in production model
Owner's experience with AB's	Farmers' knowledge of antibiotic pharmacology
Organisation of the production chain and dependency on other chains	-
Perceived efficacy	Safety and effectiveness of 3 rd and 4 th generation antibiotics
Perceived owner compliance	Veterinary treatment compliance; Antibiotic automedication
Personal beliefs regarding the veterinary contribution to antimicrobial resistance	Farmer's perception of impact of biosecurity measures
Personal preference of AB	-
Preference of broad spectrum over narrow AB's	Safety and effectiveness of 3 rd and 4 th generation antibiotics
Pressure senior veterinarians on junior colleagues	-
Pressures from politics and legislation	Enforceability of regulation of veterinary antibiotics use; Effectiveness of sector's auto-regulation
Previous clinical history of the animal	-
Professional obligation to alleviate animal suffering	-
Public health interests	Antimicrobial resistance
Public perception/opinion	Consumers' willingness to pay premium for antibiotics-free food
Rearing system (e.g. all-in-all-out pig flow)	Intensity of livestock population; Heterogeneity of livestock population.
Regulations	Enforceability of regulation of veterinary antibiotics use; Effectiveness of sector's auto-regulation
Risk and uncertainty avoidance, fear of complications (of veterinarians and farmers)	Risk of disease; Pressure on profitability
Shortcomings in advisory skills	Veterinarians' communication skills



Determinant identified in the literature	Related concepts in the systems map
Stockmanship farmer	Quality of stockmanship
Veterinarians' lacking communication and advisory skills	Veterinarians' communication skills
Veterinary surgeon's prior experience of a drug	-
Veterinarians' years of experience	-
Willingness or ability to pay AB therapy	Willingness of farmer to pay for counselling; Cost of antibiotics, Availability of cost-efficient, profitable alternative treatments
Work experience	-

AB: antibiotic(s)

Table 60 – Determinants of veterinary antibiotic choice identified from the literature and related concepts in the systems map

Determinant identified in the literature	Related concepts in the systems map
Sensitivity test results	Reliability of antibiogram testing
Veterinarians' own experience	-
Risk of ABR developing	Antimicrobial resistance
Ease of administration	Ease of application of antibiotics
Compliance	Veterinary treatment compliance; antibiotic auto-medication
Withdrawal period	Antibiotic treatment withdrawal time
Formulation	-

ABR: antibacterial resistance