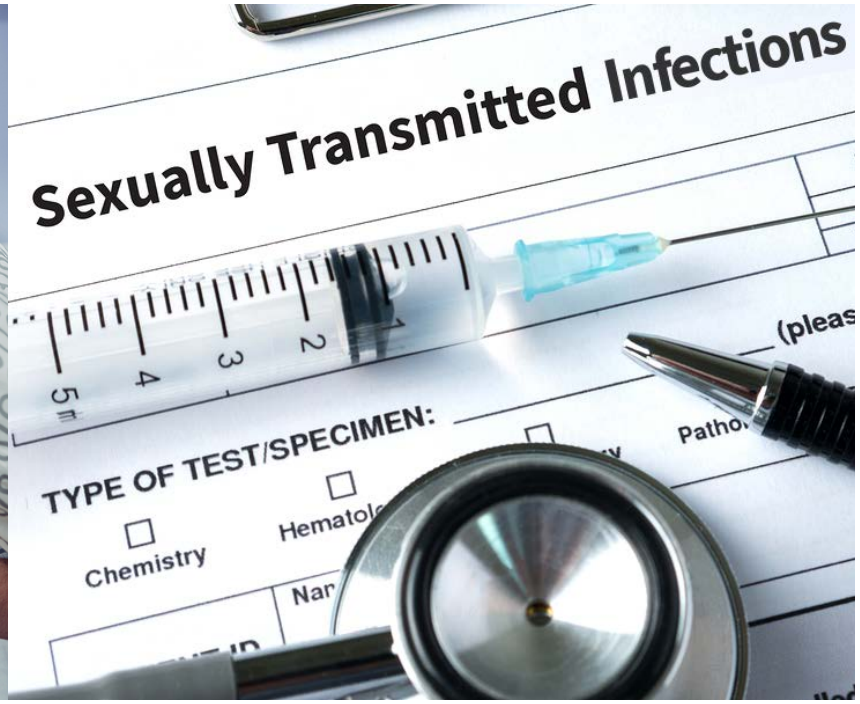
KCE REPORT 310

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

DIAGNOSIS AND MANAGEMENT OF GONORRHOEA AND SYPHILIS



KCE REPORT 310
GOOD CLINICAL PRACTICE

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AGREE	Appraisal of Guidelines Research and Evaluation
AMR	Antimicrobial resistance
BAPCOC	Belgian Antibiotic Policy Coordination Committee
BCFI – CBIP	Belgisch Centrum voor Farmacotherapeutische Informatie, Centre belge d'information pharmacothérapeutique
BIVKM – SBIMC	Belgische vereniging voor infectiologie en klinische microbiologie - Société Belge d'infectiologie et de microbiologie clinique
BPG	Benzathine Penicillin G
CDC	Centers for Disease Control and Prevention
CEBAM	Belgian Centre for Evidence-Based Medicine
CENTRAL	The Cochrane Central Register of Controlled Trials
CIA	Chemiluminescence immunoassay
CLSI	Clinical and Laboratory Standards Institute
DPP	Dual Path Platform
ECDC	European Centre for Disease Prevention and Control
EIA	Enzyme immunoassays
EMA	European Medicines Agency
EUCAST	European Committee on Antibiotic Susceptibility Testing
FDA	US Food and Drug Administration
FP	False positive
FN	False negative
FTA-ABS	Fluorescent treponemal antibody absorption test
GDG	Guideline development group

GRADE	Grading of recommendations assessment, development and evaluation
HIV	Human Immunodeficiency Virus
IM	Intramuscular
ITM – IMT – ITG	Institute of Tropical Medicine (Institut de Médecine Tropicale/Instituut voor Tropische Geneeskunde)
INAMI – RIZIV	National Institute for Health and Disability Insurance (Institut National d'Assurance Maladie-Invalidité/Rijksinstituut voor Ziekte- en Invaliditeitsverzekering)
IUSTI	International Union against Sexually Transmitted Infections
LGV	Lymphogranuloma venereum
LR	Likelihood ratio
MFI	Multiplex flow immunoassay
MIC	Minimum inhibitory concentration
MSM	Men who have sex with men
NAAT	Nucleic acid amplification tests
NGC	National Guideline Centre
NIHDI (INAMI – RIZIV)	National Institute for Health and Disability Insurance
Non-trep	Non-treponemal
NPV	Negative predictive value
PCR	Polymerase chain reaction
PICO	Participants–Interventions–Comparator–Outcomes
POC	Point of Care
PPV	Positive predictive value
QUADAS	Quality assessment tool for diagnostic accuracy studies
RCTs	Randomised controlled trials
RPR	Rapid Plasma Reagin

RR	Risk Ratio
SDA	Strand displacement amplification
SSMG	Société Scientifique de Médecine Générale
STI(s)	Sexually transmitted infection(s)
Syp	Syphilis
TMA	Transcription mediated amplification
TPPA	*T. pallidum* particle agglutination
TN	True negative
TP	True positive
Trep	Treponemal
VBOV	Vlaamse Beroepsorganisatie van Vroedvrouwen
VDRL	Venereal disease research laboratory
WHO	World Health Organization

SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Background

The incremental number of newly diagnosed sexually transmitted infections (STIs) over the past two decades in Europe is of concern. *Chlamydia trachomatis* accounts for half of the new infections, followed by gonorrhoea and syphilis being most common.[1] For these three infections the European overall rate per 100 000 persons in 2013 was, respectively, 181.7 for chlamydia, 16.9 for gonorrhoea and 5.4 for syphilis.[1]

1.1.1 Etiology, transmission, clinical features and epidemiological trends

1.1.1.1 Gonorrhoea

Gonorrhoea is caused by the Gram-negative bacterium *Neisseria gonorrhoeae* (*N. gonorrhoea*) with infection of the columnar epithelium of the urethra, endocervix, rectum, pharynx and conjunctivae.[2] Symptoms and physical signs of gonorrhoea constitute of a localised inflammation of the infected mucosal surfaces. In men, the presentation is mostly of acute urethritis with symptoms of mucopurulent urethral discharge (80%) and dysuria (50%), usually starting within 2–8 days of exposure. Asymptomatic urethral infection is uncommon in men (less than 10% of urethral infections).[2] In women, genital tract symptoms include increased or altered vaginal discharge (50%), lower abdominal pain (25%), dysuria (10–15%) and rarely intermenstrual bleeding or menorrhagia. Endocervical infection is asymptomatic in half of the cases. Rectal and pharyngeal infections are usually asymptomatic.[2]

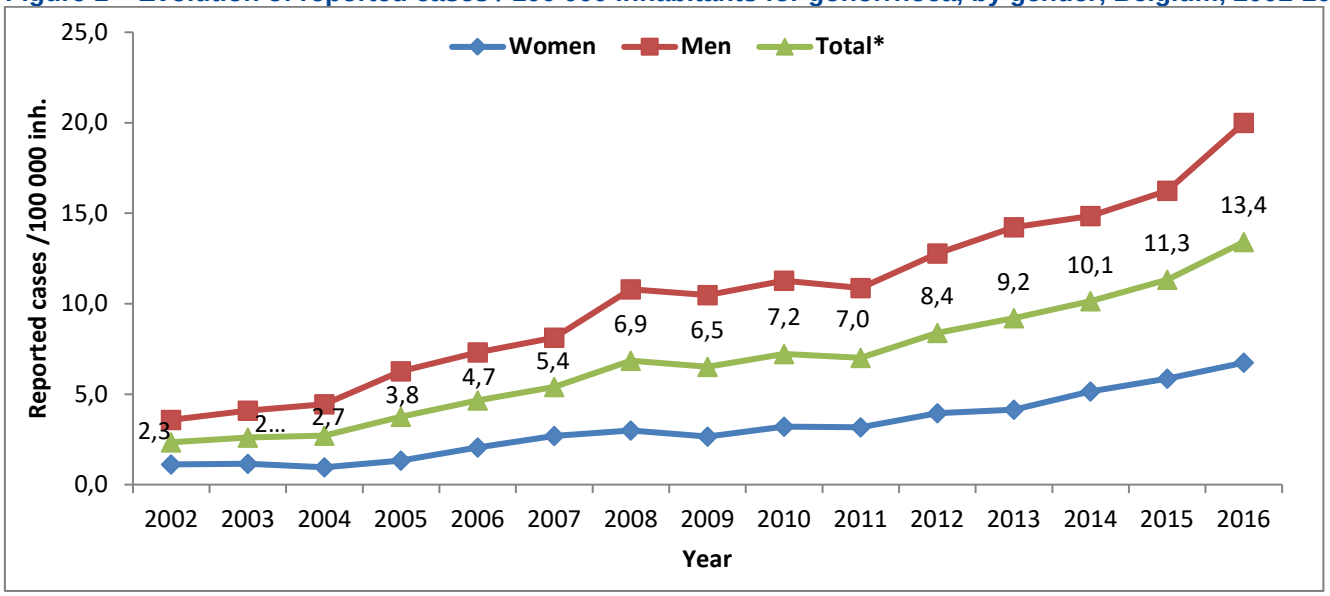
Complications can occur when the infection causes severe local symptoms of cervicitis, urethritis, proctitis or pharyngitis, or when it ascends to the upper genital tract to cause acute pelvic inflammatory disease and epididymo-orchitis or disseminate as bacteremia. A bacterial disseminated gonococcal infection can lead to arthritis or arthralgia, tenosynovitis, endocarditis, and multiple skin lesions. Chronic complications include urethral stenosis, chronic pelvic inflammatory disease, and infertility.

Transmission occurs by direct inoculation of infected secretion from one mucosa to another, i.e. genital–genital, genital–anorectal, oro-genital or oro-anal contact or by mother-to child transmission at birth.[2]

The most recent estimates of worldwide gonorrhoea by the World Health Organization (WHO) accounted to 78.3 million cases of gonorrhoea among adults in 2012.[3] In Europe, gonorrhoea with 75 349 reported cases in 2016, is the second most common bacterial STI, i.e. after chlamydial infections.[4] The significantly higher presence of symptoms in men as compared to women together with the highest number of infections in men who have sex with men (MSM) leads to a proportion of 3 infections in men versus one in women. In Europe, the highest incidence of gonorrhoea is reported among 25-34 year old adults (36.7%), directly followed by young adults (15–24 years; 35.9%); lowest rates were reported in older groups (35-44 years: 16.1% and 45+: 11.1%).[4]

In the early 1990's, there were around 65 000 reported cases of gonorrhoea in the European Union. After a significant decrease to 27 823 reported cases in 1998 and a stabilisation during a decennia, the number of reported cases constantly increased to reach a level of 75 851 reported cases in 2015.[4] Of course, this actual number may mirror a true increase as well as a better diagnosis with Nucleic Acid Amplification Tests (NAAT) combined with a better reporting of cases. In Belgium, a similar and constant increase is observed since 2002 (Figure 1). The number of cases for 2016 are reported in Table 1.

Figure 1 – Evolution of reported cases / 100 000 inhabitants for gonorrhoea, by gender, Belgium, 2002-2016



Source: Vanden Berghe et al. 2018[5] ;
*Note. *including cases for which gender was not reported; men include both heterosexuals and MSM*

Table 1 – Number of reported cases and reported cases / 100 000 inhabitants for gonorrhoea by age and gender, Belgium, 2016

Age	Reported cases		Reported cases/100 000 inhabitants	
	Women	Men	Women	Men
≤4	4	1	1.2	0.2
5-9	0	2	0.0	0.6
10-14	2	0	0.7	0.0
15-19	36	56	11.7	17.4
20-24	104	175	30.9	50.8
25-29	84	238	23.0	65.3
30-34	41	196	11.3	54.1
35-39	37	128	10.0	34.4
40-44	23	104	6.3	27.7
45-49	21	88	5.4	22.1
50-54	17	67	4.2	16.2
55-59	7	23	1.8	6.0
≥ 60	8	23	0.5	1.9
Total	384	1101	6.7	21.1

Source: Vanden Berghe et al. 2018[5]

To reduce transmission, timely and effective treatment is necessary by shortening the duration of infection and decreasing the risk of serious health sequelae, including pelvic inflammatory disease, infertility, and ectopic pregnancy.[1] Unfortunately, *N. gonorrhoea* has progressively developed resistance to the antimicrobials that are recommended as first-line treatment regimens, and current treatment options are severely limited.[1] Pharyngeal gonorrhoea is more difficult to treat probably due to lower drug levels leading to resistance development. The pharyngeal infections could serve as a reservoir and promote sustained transmission.[1] A major challenge to monitoring emerging resistant gonorrhoea is the decline in the use of gonorrhoea culture for diagnosis as NAAT testing has superseded culture. Culture techniques are required for antibiotic susceptibility testing. Currently, non-culture techniques for antibiotic susceptibility testing are nonexistent.

1.1.1.2 Syphilis

Syphilis is a systemic human disease due to infection with the spirochete bacterium *Treponema pallidum* subspecies *pallidum* (*T. pallidum*) and either acquired by direct contact with an infectious lesion, usually sexual contact, or by vertical transmission at any stage during pregnancy (highest in early pregnancy).

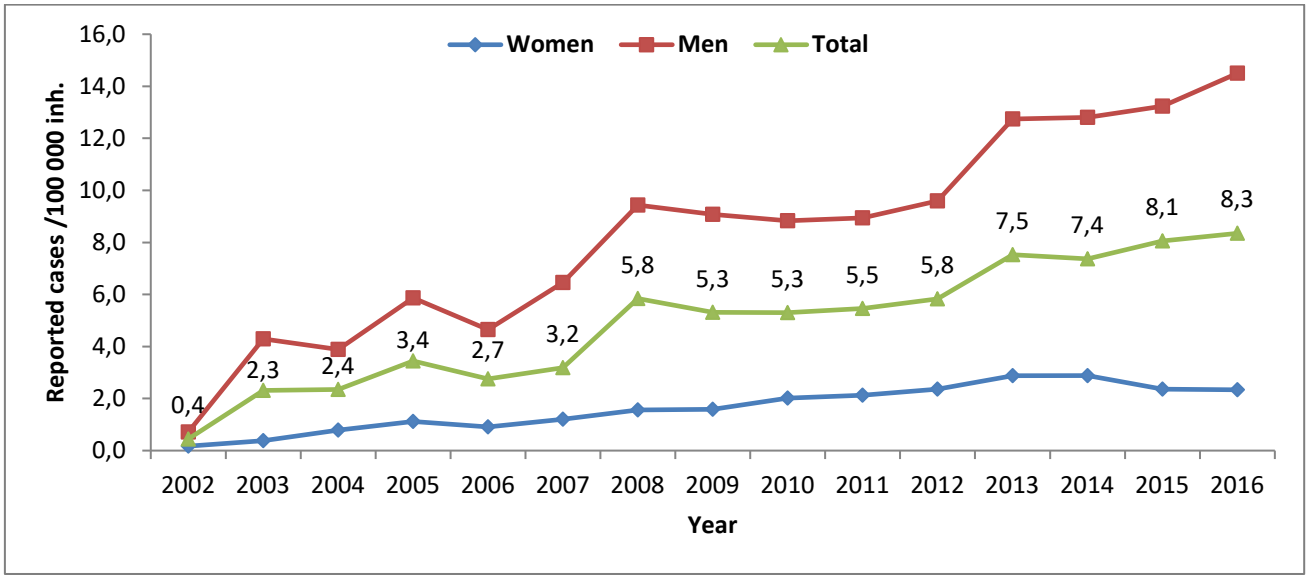
Approximately one third of sexual contacts of infectious syphilis will develop the disease.[6] Extra-genital transmission is common in MSM (ano-rectal, oral) through oral-anal or genital-anal contact. Intravenous drug use (sharing needles) and blood transfusion (rare as routine screening is performed and treponemal survival beyond 24–48h at 4°C is unlikely) are also potential routes of transmission.[6] The stages of syphilis are presented in Table 2. After infection, patients present with signs of early primary disease. Untreated, 25% of patients will develop signs of early secondary syphilis. Secondary syphilis will resolve spontaneously in 3–12 weeks and the disease enters an asymptomatic latent stage. This is defined as early within two years by WHO and within one year by the European Centre for Disease Prevention and Control (ECDC), and late thereafter (ending with the development of tertiary disease). The distinction between early and late latent disease is somewhat arbitrary, but important as approximately 25% of patients will develop a recurrence of secondary disease during the early latent stage. Late tertiary disease occurs in approximately one-third of untreated patients around 20–40 years after initial infection. The clinical manifestations of late syphilis are highly variable and are rarely seen due to the use of treponemocidal antibiotics for other indications. The evolution of reported cases for Belgium since 2002 is presented in Figure 2 and the number of cases for 2016 in Table 3.

Table 2 – Stages and symptoms of syphilis

Stage		Symptoms	Incubation and timeframe
Early	Primary Acquired past year (ECDC) Acquired past 2 years (WHO)	• Single papule and moderate regional lymphadenopathy evolves into ulcer (chancre): anogenital (penile, labial, cervical or peri-anal), single, painless and indurated with a clean base discharging clear serum but not pus • Chancres **may** also be multiple, painful, purulent, destructive, extra-genital (most frequently oral) • When present at extra-genital sites and painless, they may pass unnoticed • Ulcers resolve over 3–8 weeks	21 days (range 9-90)
	Secondary	• Widespread mucocutaneous rash and generalized lymphadenopathy • Mucous patches (buccal, lingual and genital) and highly infectious condylomata lata affecting warm, moist areas (mostly the perineum and anus) • Hepatitis; glomerulonephritis; splenomegaly; neurological complications (meningitis, hearing loss, tinnitus); uveitis, optic neuropathy, keratitis	Three months after infection 4–10 weeks after the appearance of the initial chancre
	Latent	• Asymptomatic in 75% and reoccurrence of early secondary symptoms in 25%	Up to 2 years after infection
Late	Latent	• Asymptomatic	
	Tertiary	• In one-third of untreated cases: Gummatous disease (15% of patients); cardiovascular (10%) and late neurological complications (7%)	20-40 years after initial infection

Note. Stages and symptoms of congenital syphilis were not reported in this table; ECDC: European Centre for Disease Prevention and Control

Figure 2 – Evolution of reported cases / 100 000 inhabitants for syphilis, by gender, Belgium, 2002-2016



Source: Vanden Berghe et al. 2018[5]
Note. Men include both heterosexuals and MSM

Table 3 – Number of reported cases and reported cases / 100 000 inhabitants for syphilis by age and gender, Belgium, 2016

Age	Reported cases		Reported cases/100 000 inhabitants	
	Women	Men	Women	Men
≤4	4	1	1.2	0.3
5-9	0	0	0.0	0.0
10-14	0	0	0.0	0.0
15-19	5	11	1.6	3.2
20-24	16	54	4.8	14.8
25-29	22	70	6.0	19.3
30-34	19	129	5.2	34.7
35-39	17	129	4.6	34.4
40-44	8	110	2.2	27.6
45-49	11	95	2.8	23.0
50-54	3	76	0.7	19.8
55-59	5	51	1.3	15.2
≥ 60	24	66	1.6	7.3
Total	134	792	2.3	15.1

Source: Vanden Berghe et al. 2018[5]

1.1.1.3 Chlamydia

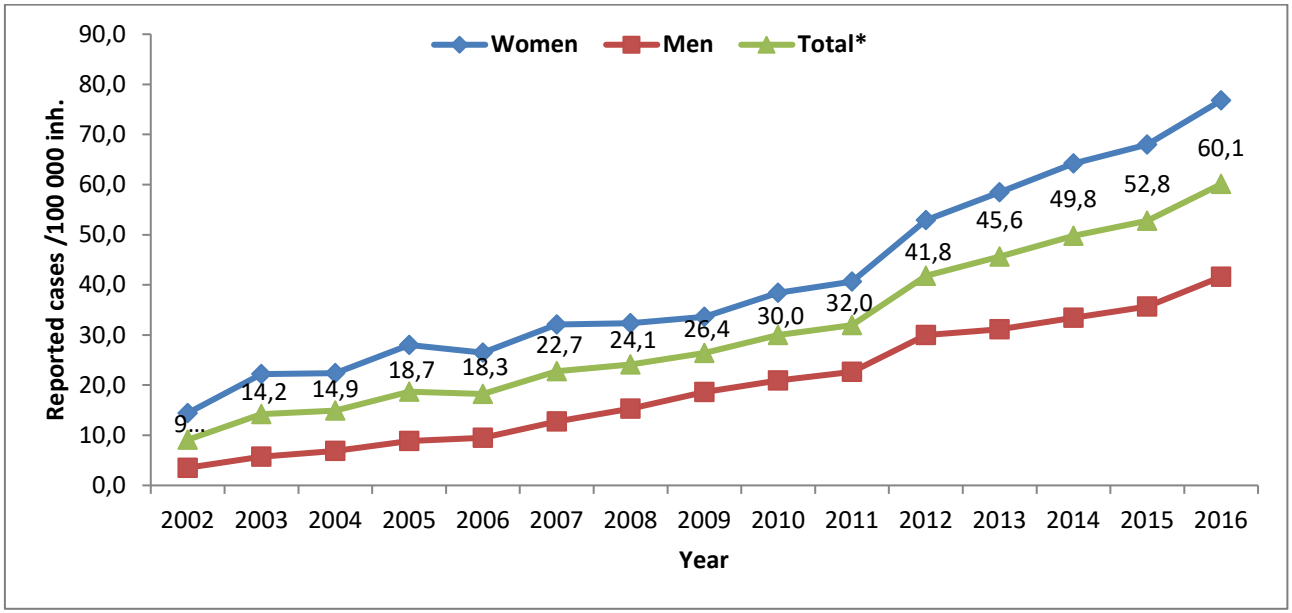
Chlamydia are caused by the intracellular bacterium *Chlamydia trachomatis* (*C. trachomatis*) with infection of the mucosal epithelium of the urethra, cervix, rectum, pharynx, endometrium, salpinx, epididymis, and conjunctivae and respiratory tract in the newborn. Several *Chlamydia* genotypes exist with three different clinical presentations: genotype D-K with the typical anogenital and ocular clinical presentation; genotypes L1, L2/L2a, L2b, L2c and L3 causing lymphogranuloma venereum (LGV), a severe anogenital infections involving the submucosa; and serotypes A-C causing the non-sexually transmitted disease trachoma, an infection of the eye leading to blindness. In the past decade, LGV has caused severe rectal infections in MSM, mostly in HIV-positive.

For non-LGV chlamydia, complications can occur when the infection ascends to the upper genital tract to cause pelvic inflammatory disease resulting in ectopic pregnancy, infertility, and chronic pelvic pain. Urogenital chlamydia infections do not result in long term immunity. Transmission occurs by direct inoculation of infected secretion from one mucosa to another, i.e. genital–genital, genital– anorectal, oro-genital or oro-anal contact or by mother-to child transmission at birth. Transmission can also occur when sex toys or other objects are used.

The most recent estimate of worldwide chlamydia by the WHO accounts to 131 million cases of chlamydia among adults globally.[7] In Europe, chlamydia is the most common bacterial STI.[8] Suboptimal diagnostics, case reporting and surveillance has meant an underestimation of the incidence. The highest incidence of chlamydia is in young adults (15–29 years; for women between 15-24 years and men 20-29 years) and, in many countries, there is a disproportionate burden of disease in ethnic minority groups with low socio-economic status and MSM.

The evolution of reported cases for Belgium since 2002 is presented in Figure 3 and the numbers of cases for 2016 in Table 4. Data on sexual preference are not collected and therefore not presented.

Figure 3 – Evolution of reported cases / 100 000 inhabitants for chlamydia, by gender, Belgium, 2002-2016



Source: Vanden Berghe et al. 2018[5]
*Note.*including cases for which gender was not reported; men include both heterosexuals and MSM*

Table 4 – Number of reported cases and reported cases / 100 000 inhabitants for chlamydia by age and gender, Belgium, 2016

Age	Reported cases		Reported cases/100 000 inhabitants	
	Women	Men	Women	Men
≤4	19	10	5.9	1.6
5-9	2	1	0.6	0.3
10-14	11	0	3.6	0.0
15-19	650	129	211.0	40.2
20-24	1606	587	477.0	170.5
25-29	1023	518	279.9	142.2
30-34	452	336	124.7	92.8
35-39	297	276	80.5	74.3
40-44	157	155	42.8	41.3
45-49	78	118	20.1	29.6
50-54	43	82	10.6	19.9
55-59	20	42	5.2	11.0
≥ 60	22	28	1.4	2.3
Total	4380	2282	76.1	43.6

Source: Vanden Berghe et al. 2018[5]

1.1.2 Notification of infectious diseases in Belgium

In Belgium, two notification systems coexist to register and monitor the evolution of different infectious diseases over time. The sentinel laboratory network, established in 1983 to obtain information on the epidemiology of infectious diseases is coordinated by Sciensano. Next to this sentinel laboratory network, other surveillance networks for human infectious diseases, complementing each other, are available in Belgium, i.e. the notification of infectious diseases organised by the Flemish Community, Brussels Capital and the French-speaking Community, the network of paediatrics collecting mainly data on vaccine preventable infectious diseases in children since 2002, the network for surveillance of sexually transmitted diseases since 2000 (Sciensano), the network of national reference laboratories and the national reference centers collecting public health microbiology data, and the registration network of general practitioners since 1979.[9] Although the mandatory notification system and the sentinel laboratory network are both fed by microbiology laboratories, additional clinical information is provided to the mandatory notification system by the treating physicians. Unfortunately the data is unlinked to the laboratory reporting. Nevertheless, Sciensano recognises a good correlation between the laboratory STI notifications and the notifications from the physicians.

1.1.2.1 Legal instruments

- Wallonia: Royal Decree 1th March 1971 about prevention of infectious diseases
- Brussels: Decree of 19 July 2007 concerning preventive health policy and decree of 23 April 2009 that report the list of infectious diseases which have to be reported
- Flanders: Decree of 21 November 2003 concerning preventive health policy listing the infectious diseases which have to be reported. The latest decree dates from 1 January 2017.

1.1.2.2 *List of notifiable diseases: Differences between communities/regions*

With the mandatory notification of major infectious diseases, the 3 Regions pursue similar objectives, i.e. to trace contacts who need vaccines, treatment, quarantine, or education; to investigate and halt outbreaks; to monitor the impact of notifiable conditions; to measure disease trends, to assess the effectiveness of control and prevention measures, to allocate resources appropriately; to formulate prevention strategies; and to detect sudden changes in disease occurrence and distribution. However, next to an identical core of infectious diseases that have to be notified, each Region added a number of further infectious diseases.

While chlamydia, gonorrhoea and syphilis have to be notified in Brussels and Flanders, only congenital syphilis needs to be notified in Wallonia.

1.1.2.3 *Channels of notification*

Three channels can be used by healthcare practitioners to notify an infectious disease. The specific channels by Region/Community are:

- For Brussels

  Phone: 0478 77 77 08 (24h/24 and 7d/7)

  Mail: notif-hyg@ccc.brussels

  Website notification (https://www.wiv-isp.be/matra/bru/connexion.aspx)

- For Flanders

  Phone: a list with the phone number and the e-mail address of the contact person per province during office hours is provided on https://www.zorg-en-gezondheid.be/contact-infectieziektebestrijding-en-vaccinatie. For urgent cases or outside of office hours, the phone number is 02 512 93 89.

  Mail: infectieziekten@zorg-en-gezondheid.be

  Website notification: https://www.zorg-en-gezondheid.be/een-meldingsplichtige-infectieziekte-aangeven

- For Wallonia

  Phone: 071 205 105

  Mail: surveillance.sante@aviq.be

  Website notification (https://www.wiv-isp.be/matra/CF/connexion.aspx)

1.2 The need for a national guideline

An early diagnosis of STIs with appropriate treatment and partner notification is fundamental for good reproductive health at an individual level and for public health in general. STI opportunistic testing, diagnosis, treatment and management belong to the core business of primary health care workers including general practitioners, sexual health clinic doctors, gynaecologists, and midwives. Other non-health professionals working at centres where groups at higher risk of acquiring STIs meet (youth workers, school sexual health advisors, and sub-Saharan migrant advisors) will be confronted with STI related questions. As currently no Belgian practice guideline exists, standards of care differ across Belgium. Overuse of tests in low risk groups and underuse in high risk groups can lead to inappropriate use of resources and poor outcomes. In the same way, inadequate treatment also leads to potentially non justified costs, increase of resistance (e.g. to specific antibiotics) and poor outcomes, including high risk for dissemination, increased transmission of other STIs including HIV, recurrence or infertility.

In the absence of a national guideline, certain clinics have developed and use their own local based testing strategies and refer to sexual health questionnaires based on Dutch, European or USA guidelines.[2, 10-13] In addition, five consensus based guidance documents were developed to inform and support the healthcare practitioners: a Domus Medica clinical practice tool for an STI consult intended for the general practitioner inclusive of a summary card (in Dutch),[14] a consultation guide for sex workers clinics (in Dutch),[15] a management guide for gonorrhoea and for syphilis (in Dutch),[16, 17] and a guide for antibiotic use (in French and Dutch).[18]

1.3 Scope

To define the scope of the clinical practice guideline for the management of STIs a scoping meeting was held with a group of experts and stakeholders, named the scoping group, on June 30th 2017. The scoping group consisted of representatives of patients (Sub-Saharan migrants) and associations devoted to STIs (e.g. GHAPRO, Sida Sol ASBL, Plateforme Prévention SIDA, Sensoa), representatives of professional associations of general practitioners and midwives (e.g. Domus Medica, SSMG, VBOV), epidemiologists and scientists from clinical settings, university faculties or scientific institutes (e.g. Sciensano, IMT/ITG, Hôpital Saint-Pierre, Bruxelles) (see colophon).

The initial demand was relatively broad and concerned all STIs along the whole pathway (testing, diagnosis, treatment) and was formulated as follows: How can existing STI practice guidelines be applied to the Belgian context with its specific target groups?

Following the scoping meeting, the focus of the Belgian guideline was restricted to:

- Primary care, more specifically the health care worker who would be the first contact of a patient with an STI or at risk of an STI;
- Opportunistic diagnostic testing in asymptomatic and symptomatic persons;
- Sexually active men and women (pregnant and non-pregnant women), including adolescents. Victims of sexual assault were excluded from this study due to particular situation and justice-related procedures.

Based on the need for a primary care STI consultation testing tool, as expressed by the scoping group, and the available resources, it was decided that the project would consist of three dimensions:

1. a 'vertical' section related to the management of patients with chlamydia, gonorrhoea or syphilis,
2. a 'transversal' clinical flow chart for a STI consultation,
3. a 'transversal' part on partner management guidance.

Table 5 – Project structure

	Content		
1	Diagnosis of chlamydia	Diagnosis of gonorrhoea	Diagnosis of syphilis
	Management of patients with confirmed diagnosis of chlamydia	Management of patients with confirmed diagnosis of gonorrhoea	Management of patients with confirmed diagnosis of syphilis
2	An STI testing consultation tool for primary practice: guidance for STI consultation and testing		
3	Partner management guidance		

The first dimension was handled by an external partner or outsourced:

- The evidence for the management of patients with chlamydia was collected, extracted and summarised by the Working group Development of primary Care Guidelines Ebpracticenet (http://www.ebpnet.be) in the context of the update of the 2004 Flemish guideline chlamydia for general practice.[19]
- The evidence for the management of patients with gonorrhoea or syphilis was collected, extracted and summarised by an external team from the National Guideline Centre (NGC) from the United Kingdom.

The second and third dimensions were performed by the KCE.

Box 1 – What is in this report and what is not?

Included in this report

In this KCE report, the reader will find the following clinical recommendations separately for **gonorrhoea** and **syphilis**:

- Assessment of risk;
- Diagnosis: Who to test, which sample to take, and which diagnostic tests to use;
- Treatment: Information and advice for the patient; timing of initiation of therapy; when to refer to second line; treatment choice in men and women, in pregnant women and in people with an allergy to a recommended antibiotic; testing and surveillance for resistance;
- Test of cure, follow-up and testing frequency;
- Notification.

In this report, the first stages of the development of a sexual health consultation instrument (methods and structure) are reported.

Not included in this report

The clinical recommendations for the management of ***Chlamydia trachomatis*** are reported in a separate report published by the Working group Development of primary Care Guidelines Ebpracticenet (http://www.ebpnet.be); this guideline can also be downloaded from the KCE Website (https://kce.fgov.be/en/publications).

The final tool (paper and online version) will be part of a further KCE report (to download from https://kce.fgov.be/en).

1.4 Remit of the guideline

1.4.1 Overall objectives

This clinical practice guideline provides recommendations for an evidence-based diagnosis and management of patients with STIs in Belgium. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences. The objective of the present clinical practice guideline is to reduce the variability in clinical practice and to improve the communication between care providers and patients.

The guideline is based on clinical evidence and may not always be in line with the current criteria for National Institute for Health and Disability Insurance (NIHDI (RIZIV – INAMI)) reimbursement of diagnostic and therapeutic interventions. The NIHDI may consider adaptation of reimbursement/funding criteria based on these guidelines.

1.4.2 Patient-centred care

The choice of a diagnostic strategy and a treatment should not only consider medical aspects but also patient preferences. Patients should be well and timely informed about all diagnostic options and all the treatment options and the advantages and disadvantages they offer. This information should be clear and repeated over time. Representatives of Sensoa and SIDA'SOS, the largest Flemish and French speaking stakeholders organisations in Belgium respectively, took part in the development of the guideline during the whole process. Patient groups were involved at the start of the project (see 1.3) and at the end during the stakeholders meeting (see Table 18).

1.4.3 Policy relevance and target users of the guideline

With an incremental number of STIs in the Belgian population each year, the impact of a new guideline will be important in terms of quality of care, standardisation of practices and resource allocation. The primary end users of this guideline are primary health care providers involved in the detection, diagnosis and management of STIs. Additionally, this guideline is highly relevant to the policy makers and contributes to the HIV 2014-2019 plan and

the future plan. This comprehensive plan formulates recommendations for testing and access to care, specifying that a national testing strategy needs to be developed for HIV and STIs in accordance with existing regulations (action 37) and that opportunistic testing by general practitioners and specialists needs to be improved (action 38). The transversal dimension of the guideline is in agreement with the integrated approach of the HIV/STI national strategy. This strategy is currently the focus of the Policy Coordination Working Group on 'sexual health and prevention' (formerly 'Inter-cabinet Working Group').

This clinical guideline is intended to be translated into handouts for consultation by all care providers involved in prevention and management of STIs including general practitioners, sexual health clinic doctors, gynaecologists, and midwives, counsellors, psychologists, sexual therapists, and non-health professionals working or volunteering in projects with high risk populations such as field workers for sex workers, MSM, transgender groups, youth, sub-Saharan migrants, migrants in general, drug users, etc. It can also be of interest for non-health professionals dealing with groups at risk for STIs and laboratory managers. In a second instance, the guideline will be implemented as an online sexual health consultation tool for guidance of a health care practitioner.

1.5 Statement of intent

Clinical Guidelines are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding the testing and management of patients with STIs.

The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all the available clinical data for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, clinical judgement and patient choice, may also be appropriate. The information in this guideline is not a substitute for proper diagnosis, treatment or the provision of advice by an appropriate health professional. It is advised, however, that significant deviations from the national guideline are fully documented in the patient's file at the time the relevant decision is taken.

1.6 Funding and declaration of interest

KCE is a federal institution funded for the largest part by INAMI/RIZIV, but also by the Federal Public Service of Health, Food chain Safety and Environment, and the Federal Public Service of Social Security. The development of clinical practice guidelines is part of the legal mission of the KCE. Although the development of guidelines is paid by KCE's budget, the sole mission of the KCE is providing scientifically valid information. KCE has no interest in companies (commercial or non-commercial i.e. hospitals and universities), associations (e.g. professional associations, unions), individuals or organisations (e.g. lobby groups) that could be positively or negatively affected (financially or in any other way) by the implementation of these guidelines. All clinicians involved in the Guideline Development Group (GDG) or the peer-review process completed a declaration of interest form. Information on potential conflicts of interest is published in the colophon of this report. All members of the KCE Expert Team make yearly declarations of interest and further details of these are available upon request.

2 METHODOLOGY

2.1 The Guideline Development Group

This guideline was developed as a result of a collaboration between a multidisciplinary group of practicing clinicians and KCE experts. The composition of the GDG is documented in Appendix 1.1 Guideline development and literature review expertise, support, and facilitation were provided by the KCE Expert Team (Appendix 1.2).

The roles assigned to the GDG were:

- To define the clinical questions, in close collaboration with the KCE Expert Team and stakeholders;
- To identify critical and important outcomes;
- To provide feedback on the selection of studies and identify further relevant manuscripts which may have been missed;
- To provide feedback on the content of the guideline;
- To provide feedback on the draft recommendations;
- To address additional concerns to be reported under a section on 'other considerations'.

2.2 International collaboration

The mutual development by KCE and NGC (Appendix 1.3) of a clinical practice guideline only concerned the search for evidence (search strategy + selection), quality appraisal, evidence tables, evaluation of the level of evidence using Grading of recommendations assessment, development and evaluation (GRADE) and the writing of the evidence report. The conclusions and the recommendations remain the sole responsibility of the KCE team.

2.3 General approach and clinical research questions

2.3.1 General approach

This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes. Several steps were followed to elaborate this guideline. Firstly, clinical questions were developed and the inclusion and exclusion criteria were defined in collaboration with members of the Guideline Development Group. Secondly, a literature review was conducted, including a search for recent, high quality guidelines as well as grey literature. The ADAPTE method was used when high-quality, recent guidelines were available that were in line with the defined PICO (see http://processbook.kce.fgov.be/node/105). An additional literature search was conducted to update the evidence retrieved from the guidelines and to answer research questions not covered by the guidelines (e.g. combined diagnostic tests for gonorrhoea and chlamydia).

After having decided to restrict the scope of the guideline to chlamydia LGV, chlamydia non-LGV, gonorrhoea, and syphilis managed in primary care settings, the following broad research questions were withheld by the scoping group:

To be answered for chlamydia LGV, chlamydia non-LGV, gonorrhoea, and syphilis

- What is the clinical picture, diagnosis, treatment and management, inclusive of follow-up, and schedule of retesting, of the STI?

What is the content and clinic flow for an STI primary care consultation?

- How can opportunistic STI testing be offered?
- What are the questions to ask for to identify risks and identify which tests to perform?
- Which tests are to be performed for a pre-defined risk group?
- Which specimen site(s) and test type is performed according to each STI?

How is good partner management performed?

- What are the process steps in partner(s) management?
- How are the patient contacts identified?
- What are the lookback periods?
- And how is/are this/these partner(s) notified and managed?

The selection of research questions was made by the KCE team and members of the GDG at the first GDG meeting held on 26th January 2018.

The questions on the management of patients with confirmed diagnosis of chlamydia were developed by the Belgian Working group Development of Primary Care Guidelines – Ebpracticenet.

The research questions for the diagnosis and management of chlamydia, gonorrhoea and syphilis were to be answered by a strict evidence based approach using a standard methodology based on a systematic review of the evidence (as mentioned above). The clinical picture, follow-up and schedule of retesting were based on the content of a critical analysis from the selected guidelines with the AGREE-II. The remaining research questions on the flow of an STI consultation and the partner notification were answered on the basis of a critical analysis approach. This critical analysis is considered an implementation step of the diagnosis and treatment research questions (first dimension), adding in extra information from the critical analysis to arrive to a sexual health consultation focused on the testing of STIs for primary care. The critical analysis is summarised under the implementation section. The research questions were translated into in- and exclusion criteria using the PICO (Participants–Interventions–Comparator–Outcomes) framework and are described below.

2.3.2 Research questions

Table 6 – Research questions and PICO

	Diagnostic accuracy review for gonorrhoea
Objective	To determine the most accurate tests (laboratory detection methods) for diagnosing gonorrhoea for men and women, including consideration of sample type (cervical, vaginal, urethral, urine, rectal, pharyngeal).
Review questions	What are the diagnostic tests of choice for diagnosis of gonorrhoea in primary care? What are their respective diagnostic characteristics by gender?
Population	Included: Symptomatic or asymptomatic sexually active men and women (pregnant and non-pregnant), including adolescents. Excluded: victims of sexual abuse*; Countries outside of Europe, US, Canada, and Australia.
Intervention	Included: Tests that detect gonorrhoea in biological specimens from various anatomical sites (urine, endocervix, urethra, vagina, anus, and pharynx). Following tests should also be included: self-collected tests, such as auto tests and online tests, point of care (PoC) tests, and combination test for gonorrhoea and chlamydia. Following strategy: Diagnostic Accuracy of Test on Pooled Specimens from different anatomical sites from one individual. This type of studies investigates individual tests for each different sample and the one pooled sample against the reference standard. Excluded: sample from glans penis, Papanicolaou sample for cervical cancer screening, the following tests are not used in Belgium: BINAX NOW, NG Biostar, LDQA targeting porA pseudomgene, Bio Rad Dx assay, real time porA assay
Comparator	Included: Culture or expanded reference standards (i.e. positive result on two nonculture tests, positive result on two different specimens, or positive result on the original test and a confirmatory test). Excluded: none
Outcomes	Included: Diagnostic accuracy including the (potential) benefits of pooling of the specimens from different anatomical sites: True positives (TP), False positives (FP), False negatives (FN), True negatives (TN), Sensitivity (%), Specificity (%), Positive predictive value (PPV) (%), Negative predictive value (NPV) (%), Likelihood ratios (LR) Clinical outcomes: Harmful effects (such as pain, discomfort), user-friendly aspects of tests Excluded: Studies in which it is not possible to calculate diagnostic characteristics of the tests.
Study design	Included: • Good-quality systematic reviews, diagnostic randomized control trials, prospective and retrospective diagnostic cohort studies, in which the index test(s) and the reference standard test are applied to the same patients in a cross-sectional design. • Articles in Dutch, English and French were included. Excluded: • Two-gate/case-control study designs - cross-sectional studies which compare the results of the index test in patients with an established diagnosis with its results in healthy controls. • Case control studies. • Narrative reviews. • Case reports.

	• Studies presented as conference abstract only. If no full-text was available, the study was not taken into account for the final recommendations.
	Intervention review on the management of gonorrhoea
Objective	To determine the most effective treatment for uncomplicated gonorrhoea, including during pregnancy, and whether different considerations are required in case of allergy.
Review questions	What is the recommended treatment for uncomplicated gonorrhoea of the urethra, cervix, rectum and pharynx in sexually active women and men including adolescents? What is the recommended treatment for uncomplicated gonorrhoea of the urethra, cervix, rectum and pharynx in pregnant women? What is the recommended treatment for uncomplicated gonorrhoea of the urethra, cervix, rectum and pharynx in case of allergy to cephalosporin?
Population	Included: symptomatic or asymptomatic sexually active women (pregnant and non-pregnant) and men, including adolescents. Strata (reviewed separately): • Pregnant women • People with severe cephalosporin allergy Excluded: victims of sexual abuse (studies that included victims in their sample will not be excluded), children, countries outside of Europe, US, Canada, and Australia to be excluded as prevalence and practice are different.
Intervention	Included: Antibacterials to treat gonorrhoea Excluded: Penicillin and quinolones
Comparator	Included: Compared to other interventions Excluded: Penicillin and quinolones
Outcomes	Critical: Number cured and adverse events (including: nausea, diarrhoea, vomiting, abdominal pain, adverse events in babies) Important: Compliance, antimicrobial resistance and adverse events (including: dyspepsia, fatigue, dizziness and tendon disorder).
Eligibility criteria – study design	Systematic reviews, Randomised controlled trials. In the event of insufficient data from randomised controlled trials (RCTs), observational trials will be considered, with adjustment for appropriate confounders in a multivariate analysis.

	Diagnostic accuracy review for syphilis
Objective	To determine the most accurate tests, and most appropriate strategy, for diagnosing syphilis in men and women.
Review questions	What are the diagnostic tests of choice for diagnosing syphilis in primary care? What is the accuracy of currently used screening tests and strategies (e.g. sequence of tests) for detecting syphilis infection?
Population	Included: Symptomatic or asymptomatic, sexually active men and women (pregnant and non-pregnant), including adolescents. Excluded: Children, countries outside of Europe, US, Canada and Australia and victims of sexual abuse (studies which included victims in their sample will not be excluded).
Intervention	Included: Tests that detect syphilis in biological specimen (Polymerase chain reaction (PCR) and test kits included)

	Strategies of different test sequences (compared to each other) will be reviewed as a separate strata. Excluded: Laboratory detection methods for the visual demonstration of *T. pallidum*. Tests used for confirming or excluding neurosyphilis, cardiovascular syphilis, ocular syphilis and auricular syphilis.
Comparator	Included: Traditional algorithm and reverse algorithm and any combination with confirmatory tests Comparison to other molecular tests Excluded: Not compare off and on site tests
Outcomes	Included: Diagnostic accuracy measures: True positives (TP), False positives (FP), False negatives (FN), True negatives (TN) Sensitivity (%), Specificity (%), PPV (%), NPV (%), Likelihood ratios Clinical outcomes: Harmful effects (such as pain and discomfort), User-friendly aspects of the tests Excluded: Studies in which it is not possible to calculate diagnostic characteristics of the tests will be excluded.
Study design	Included: Good-quality systematic reviews; diagnostic randomized control trials; prospective and retrospective cohort studies, in which the index test(s) and the reference standard test are applied to the same patients in a cross-sectional design Exclusions: Two-gate/case-control study designs - cross-sectional studies which compare the results of the index test in patients with an established diagnosis with its results in healthy controls. Case control studies will be excluded.
	Intervention review on the management of syphilis
Objective	To determine the most effective treatment for uncomplicated syphilis in adults
Review questions	What is the recommended therapy for uncomplicated syphilis in sexually active women and men including adolescents? What is the recommended treatment for uncomplicated syphilis in case of allergy to penicillin?
Population	Sexually active women and men, including adolescents Exclusions: pregnant women**; victims of sexual abuse*, newborns (congenital syphilis)
Intervention	Antibiotics to treat syphilis.
Comparator	Compared to each other. Different dose regimens will be compared.
Outcomes	Critical: clinical cure, serological response, side-effects including allergy and toxicity Important: antimicrobial resistance, compliance
Study design	Systematic reviews, Randomised controlled trials. In the event of insufficient data from RCTs, observational trials will be considered, with adjustment for appropriate confounders in a multivariate analysis. Animal model studies will be excluded.
	Diagnostic accuracy review for chlamydia
Objective	Determination of the most accurate tests for the diagnosis (laboratory detection) of a *Chlamydia trachomatis* infection in men and women, including consideration of the sample type (cervical, vaginal, urethral, urinary, anorectal, oropharyngeal)

Review questions	What are the recommended tests for the diagnosis of a urogenital, oropharyngeal and anorectal *Chlamydia trachomatis* infection in sexually active men and women (including pregnant women) and adolescents?
Population	Included: symptomatic and asymptomatic sexually active men and women, including adolescents and pregnant women Excluded: victims of sexual abuse (but publications/studies with such participants as part of the sample were not excluded), children
Intervention	Included: (1) tests that detect *Chlamydia trachomatis* in biological samples from different anatomical sites (endocervix, vagina, urethra, urine, anus/rectum, pharynx) (2) tests for self-collection, PoC tests = tests that diagnose a chlamydia trachomatis infection in first-line practice (i.e. no laboratory detection) and pooling (urogenital, oropharyngeal or anorectal) samples from the same patient
Comparator	Included: comparison with culture or other standards (e.g. serum testing) Excluded: none
Outcomes	Included: (1) diagnostic accuracy (sensitivity, specificity, false positives, false negatives, positive predictive value, likelihood ratio) (2) patient comfort (3) ease of use
Study design	Included: systematic reviews (and meta-analyses), diagnostic RCTs and cohort studies - Studies published in English, French, German or Dutch Excluded: studies for which no full text was available via Belgian Centre for Evidence based Medicine (Cebam)/University of Ghent (only an abstract), narrative reviews, case reports - Studies in all other languages
	Intervention review on the management of chlamydia
Objective	(1) Determining the most effective treatment of an uncomplicated *Chlamydia trachomatis* infection (2) Determination of the most effective treatment of an LGV infection (3) Determining the recommended follow-up of patients with chlamydia infection (4) Determining the recommended follow-up of patients with LGV infection
Review questions	(1) What is the recommended treatment for an uncomplicated urogenital, oropharyngeal and anorectal chlamydia trachomatis infection in sexually active men and women (including pregnant and breastfeeding women) and adolescents? (2) What is the recommended treatment for LGV infection in sexually active men and women (including pregnant and breastfeeding women) and adolescents? (3) What is the recommended follow-up of sexually active men and women (including pregnant and breastfeeding women) and adolescents after the treatment of a chlamydia infection: test of cure and any additional advice? (4) What is the recommended follow-up of sexually active men and women (including pregnant and breastfeeding women) and adolescents after the treatment of an LGV infection: test of cure and any additional advice?
Population	Included: symptomatic and asymptomatic sexually active men and women, including adolescents, pregnant women and breastfeeding women

	Excluded: victims of sexual abuse (but publications/studies with such participants as part of the sample were not excluded), children
Intervention	Antibiotics for the (medicinal) treatment of chlamydia / LGV
Comparator	Included: comparison with other interventions = comparison between different antibiotic treatments Excluded: none
Outcomes	Effectiveness of treatment, compliance, side effects, antimicrobial resistance
Study design	Included: Systematic reviews (and meta-analyses), RCTs, observational studies - Studies published in English, French, German or Dutch Excluded: studies for which no full text was available via Cebam/University of Ghent (only an abstract) - Studies in all other languages
	Referral of patients with a chlamydia infection
Objective	(1) Determining situations in which a referral to second line care of a patient with a chlamydia infection is appropriate. (2) Determining situations in which a referral to second line care of a patient with an LGV infection is appropriate.
Review questions	(1) In what situations is it recommended to refer a patient with a chlamydia infection to second line care? (2) In what situations is it recommended to seek additional advice from a physician-specialist regarding a patient with a chlamydia infection? (3) In what situations is it recommended to refer a patient with an LGV infection to second line care? (4) In what situations is it recommended to seek additional advice from a physician-specialist regarding a patient with an LGV infection?
Population	Included: following patients diagnosed with a chlamydia or LGV infection: symptomatic and asymptomatic sexually active men and women, including adolescents, pregnant women, breastfeeding women Excluded: victims of sexual abuse (but publications/studies with such participants as part of the sample were not excluded), children (but publications/studies advising on the follow-up of neonates from mothers with a chlamydia trachomatis infection were not excluded)
Intervention	Treatment and/or follow-up in second-line care
Comparator	Excluded: none
Outcomes	/
Study design	Included: All publication types/study designs - Studies published in English, French, German or Dutch Excluded: Publications of which no 'full text' was available via Cebam/University of Ghent (only an abstract) - studies in all other languages
	Developing an STI consultation tool for primary practice
Objective	To define the content and steps of sexual health STI testing consultation in primary care
Research questions	How can opportunistic STI testing be offered? Which are the questions to ask for to identify risks and identify which tests to perform? Which tests are to be performed for a pre-defined risk group? Which specimen site(s) and test type is performed according to each STI?
Population	Included: Symptomatic or asymptomatic sexually active men and women (pregnant and non-pregnant), including adolescents Excluded: Children age <15 years; victims of sexual abuse

Intervention	Included: STI consultation and guide for interviews in primary care Excluded: algorithm to identify the diagnostic tests
Comparator	No comparator
Outcomes	Included: algorithm to structure the consultation according to the initial reason to consult.
Study Design	Guidelines, reviews, algorithms in STI guides and STI tools used in clinical setting or community-based settings
	Review of interventions for Partner management
Objective	To determine strategies for the management of partner(s) of patients with a diagnostic confirmation of STI.
Research question	What are the process steps in partner(s) management? How are the patient contacts identified? What are the lookback periods? And how is/are this/these partner(s) notified and managed?
Population	Included: Management of partners of patients with confirmed diagnosis of an STI (symptomatic or asymptomatic, sexually active men and women (pregnant and non-pregnant), including adolescents. Exclusions: victims of sexual abuse*
Intervention	Included: Interventions that describe the process of partner management, e.g. identifying contacts of a person infected by an STI and referral to a health care provider for appropriate management.
Comparator	No comparator
Outcomes	Included: patient initiated referral; provider initiated referral; dual referral; third party referral; testing reminders; patient delivered therapy; patient information; contact methods; anonymous contact tracing; health care referral; public health referral; barriers for referral; novel partner notification practices; partner notification plan; tools for partner referral; contract referral
Study design	Guidelines, reviews; tools; guidance documents for general practitioners

** No specific search will be performed for this population but studies which included victims in their sample will not be excluded. A textbox will be added to the guideline to clarify that these patients could need an additional management approach (e.g. judicial procedures) on top of the diagnostic testing as described in this research question.*
*** Outcomes for syphilis treatment: this guideline only concerns primary care and pregnant women are referred to secondary care due to the complicated aspects of the syphilis treatment, particular in this patient group.*

2.4 Search for guidelines and quality appraisal

2.4.1 Databases and date limits

A literature search was performed by the information specialist (Nicolas Fairon, KCE) to inform the scoping meeting on the existence of high quality guidelines. After the scope was defined, the same information specialist repeated the search which was elaborated to cover the full content of the scope of the guideline. The original literature search on Medline identified general broad STI guidelines, chlamydia, syphilis, gonorrhoea infection specific guidelines, and guidelines covering the STI consultation and the partner management. The second elaborated search included a search for populations with high STI risk behaviour with the search engines Medline Ovid, The Cochrane Database of systematic reviews (http://www.cochrane.org), and Embase (http://www.embase.com/). This elaborated search included guidelines, systematic reviews, health technology reports, STI algorithms and articles addressing STI risk factors published from 2005 onwards. Further, the following grey searches were included in the literature search:

- Haute autorité de la santé, France: https://www.has-sante.fr/portail/jcms/fc_1249693/en/piliers;
- Canadian agency for drugs and technologies in health: https://www.cadth.ca/fr;
- Swedish Council on Health Technology Assessment: http://www.sbu.se/en/;
- Centers for disease control (CDC): https://www.cdc.gov/std/;
- the Institut für qualität und wirtschaftlichkeit im gesundheitswesen: https://www.iqwig.de/;
- OpenAire reports;
- the National Institute for Health and Care Excellence: http://www.nice.org.uk/;
- the Agency for healthcare research and quality: (via the National Guideline Clearinghouse website; http://www.guideline.gov/);
- Greylit.org;
- Opengrey;
- the Guideline International Network database: (http://www.g-i-n.net);
- WHO: http://www.who.int/reproductivehealth/publications/rtis/en/;

The following websites identified by the stakeholders were then searched by one researcher (Vicky Jespers, KCE):

- Domus Medica https://www.domusmedica.be/;
- Ghapro http://www.ghapro.be/en/index.html;
- Agentschap Zorg en gezondheid Vlaanderen https://www.zorg-en-gezondheid.be/;
- Tijdschrift voor de geneeskunde http://www.tvg.be;
- Nederlands tijdschrift voor geneeskunde: https://www.ntvg.nl/search/advanced;
- Nederlands huisartsen genootschap https://www.nhg.org;
- Nederlandse Vereniging voor Dermatologie en Venereologie www.huidarts.info.
- The electronic search for systematic reviews, meta-analyses and guidelines covered the period until 11/01/2018.

Further information about ongoing research was obtained by contacting study authors and organisations. The European Medicines Agency (EMA) website was consulted to find all information about the authorisation for medicines. Members of the GDG were also consulted to identify relevant evidence that might have been missed during the search process.

2.4.2 Search strategy

A combination of appropriate MeSH terms and free text words was used (for the full strategy see Appendix 2.1). The MeSH terms for the initial search informing the scoping meeting were: “sexually transmitted disease”, “guideline, "2005-Current", and excluding “HIV”. The following search terms were added for the elaborated search: “chlamydia”, “gonorrhoea”, “syphilis”, “hepatitis B”, “hepatitis C”, “men who have sex with men”, “immigrant”, “adolescent”, “young adult”, and “sex worker”. The elaborated search results were used firstly, to select high quality guidelines to be used as the basis for the final search for the diagnosis and management of gonorrhoea and syphilis (section 2) and secondly, for section 1 (tool) and section 3 (partner management).

The 3504 search hits were screened on title and abstract by one researcher (Vicky Jespers, KCE) with the PICO and in- and exclusion criteria. First, the titles and abstracts of the identified documents were checked and irrelevant hits were eliminated. After the elimination of duplicates, 90 citations were selected on the basis of title and abstract addressing the scope of the project. An additional 63 records were identified through a grey literature search and the websites as mentioned above. After excluding 42 records (outdated version 24, surveillance paper 2, out of scope 16), we retained 111 documents for full-text reading. Of those 111, 14 documents were excluded (old version of a guideline: n=1, guidelines published before 2011: n=11; out-of-scope documents: n=2) (see Appendix 2.1.4).

The search strategies for the diagnosis and management of gonorrhoea and syphilis, conducted by NGC, are detailed in Appendix 2.2 through Appendix 2.5. The search strategy for chlamydia will be available through the website of the ‘Working group Development of primary Care Guidelines’ and is not presented in this report (http://www.ebpnet.be).

2.4.2.1 Identification and retrieval of guidelines for gonorrhoea / syphilis

A total of 8 guidelines were identified for gonorrhoea of which 5 were dedicated to gonorrhoea [2, 12, 20-22], 2 were comprehensive guidelines [23 24] and one covered both gonorrhoea and chlamydia [25, 26] (see Appendix 3.1). A total of 8 guidelines were identified for syphilis of which 6 were dedicated to syphilis [6, 10, 11, 27-30], and 2 were comprehensive guidelines [23, 24] (see Appendix 3.2). As mentioned above in the search strategy, the guidelines before 2011 were considered outdated by the GDG and therefore not selected.

2.4.2.2 Identification and selection of guidance documents for the STI consultation tool

A total of 20 documents were retained, providing guidance or algorithms useful to guide a consultation in primary care (see Appendix 4).

One well developed online tool for an STI consultation was selected by the GDG and the KCE team: the Australian New South Wales government “STI/HIV testing tool: easy as 1 2 3” updated in September 2017 (https://stipu.nsw.gov.au/wp-content/uploads/STI-HIV-Testing-Tool-online.pdf).

The main reasons for this choice were: the scope of the tool, its applicability to the Belgian situation, the clarity of presentation, its recent update and the yearly revision of the tool. This tool covers three main topics answering the following questions: ‘Starting a conversation about sexual health testing’; ‘STI/HIV testing table (describing the patient and specific risk groups)’; ‘How to test – Infection, specimen site and test type’; ‘Contact tracing’. The tool is set in a way to list for each of the risk groups, the commonly encountered infections and the timeframe how often the patient should be tested. The specimen collection site is further described by gender for each infection including the preferred test.

2.4.2.3 *Identification and selection of guidance documents for partner management*

A total of 12 documents were retained, providing guidance for the management of partners with an STI in a consultation in primary care (see Appendix 5). Some of the consultation tools identified above were consulted as well.

2.4.3 *Quality appraisal*

The Appraisal of Guidelines Research and Evaluation (AGREE) II instrument was used to evaluate the methodological quality of the identified international guidelines (www.agreetrust.org) (see Appendix 6.1.1). We evaluated the comprehensive STI guidelines and the guidelines focusing on gonorrhoea and/or syphilis. Each guideline was scored by two independent researchers (Vicky Jespers and Sabine Stordeur, KCE) and the points of difference were discussed and reviewed in case of disagreement to come to a final score.

Based on this overall assessment with AGREE, 6 high quality guidelines were retained covering diagnosis and/or management of gonorrhoea see appendix 6.1.1). The systematic review prepared by Nelson et al. (2014) for the U.S. Preventive Services Task Force clinical guideline was appraised as the most recent review of high quality.[25, 26] A limitation was the exclusion of rectal, oropharyngeal, and self-administered specimens outside the clinical setting as only test cleared by the U.S. Food and Drug Administration were considered.

The evaluation with AGREE of guidelines covering diagnosis and/or management of syphilis led us to select 6 high quality guidelines with an overall quality score above 7.5 (see Appendix 6.1.1). The systematic review prepared by Cantor et al. (2016) for the U.S. Preventive Services Task Force was appraised as the most recent review of high quality.[29] The International Union against STIs (IUSTI) guideline 2014[11] that obtained a slightly lower score of 7.3 was also included as it encompasses the adapted reverse laboratory testing algorithm for syphilis, not currently recommended by the US guidelines, but which is currently applied in Belgium next to the other algorithms.

2.5 Additional literature search: diagnostic tests for gonorrhoea

2.5.1 *Diagnostic tests of choice for diagnosis of gonorrhoea in primary care*

2.5.1.1 *Selection of systematic reviews*

On 11/01/2018 a search was performed to identify systematic reviews comparing tests for diagnosis of gonorrhoea versus culture or expanded reference standards in asymptomatic and symptomatic men and women (from 2004 to 11/01/2018). MEDLINE and Cochrane were searched. Furthermore, all systematic reviews of the Cochrane Central Group were browsed for their relevance.

In MEDLINE 663 potential relevant references were identified. After de-duplication 616 references remained. Four systematic reviews were ordered for screening but excluded. The searches in the Cochrane databases resulted in 224 relevant systematic reviews, of which 202 were unique references.

Studies were screened on **title and abstract** by two researchers (Clare Jones and Sedina Lewis, NGC) with the PICO in- and exclusion criteria. In case of doubt the content experts were consulted. First, the titles and abstracts of the identified studies were checked and irrelevant studies were eliminated. In a second step, the remaining papers were screened by reading their **full-text**. If no full-text was available, the study was excluded for the final recommendations. Reference lists of the selected studies were hand searched for additional relevant manuscripts.

The screening of the **guidelines** was performed on title and abstract by a group of two researchers (Clare Jones and Sedina Lewis, NGC) based on the PICO in- and exclusion criteria.

2.5.1.2 Selection of primary studies for diagnosis

On 11/01/2018 a search was performed to identify RCTs and observational studies comparing tests that detect gonorrhoea versus culture or expanded reference standards in symptomatic or asymptomatic sexually active men and women including adolescents aged 15 and older. MEDLINE (including PreMedline) and The Cochrane Central Register of Controlled Trials (CENTRAL) were searched, without data limits. 887 potential relevant references were identified. After de-duplication, 835 references remained, upon which 3 papers retrieved from other sources were added (n=838). Based on title and abstract 716 studies were excluded. Of the remaining 122 references, 118 were primary studies and 4 were reviews. Of these, 18 original studies were included (Table 7) and the remaining 104 references were excluded with reason (see Appendix 2.2.4).

Table 7 – Diagnostic tests for gonorrhoea - Included observational studies

Reference	Diagnostic tests
Chernesky 2005[31]	Transcription mediated amplification (TMA) and Aptima
Cosentino 2012[32]	TMA Aptima Combo 2, Stand displacement amplification test (SDA) Becton Dickinson's (BD) ProbeTec and culture
Fang 2018[33]	SDA BD ProbeTec
Gaydos 2010[34]	Polymerase chain reaction (PCR) Abbott Realtime CT/NG, TMA Aptima Combo 2 and SDA BD ProbeTec.
Gaydos 2013[35]	PCR GeneXpert CT/NG assay
Masek 2009[36]	SDA BD ProbeTec, TMA Aptima Combo 2 and PCR Roche amplicor
Moncada 2004[37]	TMA Aptima Combo 2, Ligase Chain Reaction Assay (LCR), Culture
Moncada 2009[38]	TMA Aptima Combo 2, SDA BD ProbeTec, Culture
Ota 2009[39]	SDA BD ProbeTec ET system
Rumyantseva 2015[40]	PCR AmpliSens multiplex real-time
Schachter 2005[41]	TMA Aptima Combo 2
Schachter 2008[42]	SDA BD ProbTec, TMA Aptima Combo 2, Culture
Stewart 2012[43]	TMA Aptima Combo 2 and culture
Sultan 2016[44]	TMA Aptima Combo 2 (pooled versus non-pooled)
Taylor 2012[45]	PCR Roche Cobas 4800, TMA Aptima Combo 2 and SDA BD ProbeTec
Van Der Pol 2012a[46]	PCR Roche Cobas 4800, TMA Aptima Combo 2, SDA BD Viper ProbeTecGC Qx
Van Der Pol 2012b[47]	SDA BD Qx Amplified Assay
Van Der Pol 2017[48]	BD Max GC assay

2.5.2 Quality appraisal

Critical appraisal of each primary study was performed by a single researcher, and quality assured by a second researcher. Retrieved diagnostic studies were assessed for the risk of bias by means of the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. The four domains assessed for risk of bias were patient selection, index test, reference standard, and flow and timing. Applicability concerns were assessed in the first three domains. In each domain, we answered the signalling questions with 'Yes', 'No', or 'Unclear' and for each domain judged the risk of bias as 'Low', 'High', or 'Unclear' risk. The overall quality of evidence was summarised using GRADE methodology recommended for diagnostic tests.[49]

The tools used for the quality appraisal and the results of the quality appraisal are presented in the Appendix 6.1.2. The GRADE rating was applied to the 18 selected primary studies; of them, 5 studies were rated 'no serious risk of bias', 8 were rated 'serious risk of bias' and the last 5 studies were rated 'very serious risk of bias' (see Appendix 6.1.2, Table 11).

2.6 Additional literature search: treatment for gonorrhoea

2.6.1 Treatment for gonorrhoea in primary care

2.6.1.1 Search strategy

On 19/02/2018 and 22/02/2018 a search was performed to identify systematic reviews and primary studies comparing treatment of gonorrhoea in men and women including young people. This search strategy was an update from the WHO 2016 STI guideline[22] as this review question used this guideline as baseline.

The following databases were included in the literature search:

- The Cochrane Database of systematic reviews (http://www.cochrane.org) (2015-19/02/2018)
- Medline (http://www.ncbi.nlm.nih.gov/pubmed) (2015-19/02/2018)
- Embase (http://www.embase.com/) (2015-19/02/2018)
- PubMed (09/03/2013-22/02/2018)

A combination of appropriate MeSH terms and free text words was used (Appendix 2.3).

For the first search:

- Pathology: **gonorrhoea OR gonorrhea OR gonococcal;**
- Field of search (intervention): Ceftriaxone, according to the research questions.
- Type of reference (study design) included: **(systematic) reviews OR meta-analyses OR guidelines OR RCT's OR diagnostic trials OR controlled clinical trials**

For the second search:

- Pathology: **gonorrhea OR gonorrhoeae OR gonorrhoea OR gonococcus OR gonococcal**
- Field of search (intervention): treatment or therapy or resistance or antibiotics or failure, according to the research questions.
- Type of reference (study design) included: **(systematic) reviews OR meta-analyses OR guidelines OR RCT's OR diagnostic trials OR controlled clinical trials**

Studies were screened on **title and abstract** by a group of two researchers (Clare Jones and Sedina Lewis) with the PICO in- and exclusion criteria. In case of doubt the content experts were consulted. First, the titles and abstracts of the identified studies were checked and irrelevant studies were eliminated. In a second step, the remaining papers were screened by reading their **full-text**. If no full-text was available, the study was excluded for the final recommendations. Reference lists of the selected studies were hand searched for additional relevant manuscripts.

The screening of the **guidelines** was performed on title and abstract by a group of two researchers (Clare Jones and Sedina Lewis) based on the PICO in- and exclusion criteria.

2.6.1.2 Selection of systematic reviews and primary studies

In MEDLINE, Embase, PubMed and Cochrane 2047 potential relevant references were identified. After de-duplication 1884 references remained. Based on title and abstract 1876 studies were excluded resulting in 7 remaining studies (4 systematic reviews and 3 primary studies) from the update search.

Systematic reviews: Of the 4 remaining reviews, 1 systematic review (Cochrane review) was included as background information only as the included primary studies were extracted separately (Table 8). The remaining 3 systematic reviews were excluded with reason (Appendix 2.3.5.).

Primary studies: In addition to the 3 primary studies selected there was an additional 47 primary studies selected through other methods for consideration. Of these 50 studies, 6 studies were included (Table 9) and 44 studies were excluded with reason (Appendix 2.3.5.).

Further information about ongoing research was obtained by contacting study authors and organisations. The EMA website was consulted to find all information about the authorization for medicines. Members of the GDG were also consulted to identify relevant evidence that might have been missed during the search process.

Table 8 – Treatment for gonorrhoea - Included systematic reviews

Reference	Interventions
Comunian-Carrasco 2018[50]	Cochrane Review included RCTs from Cavenee and Ramus (see Table 9**)**

Table 9 – Treatment for gonorrhoea - Included RCTs

Reference	Treatment	Interventions
Cavenee 1993[51]	Single	Ceftriaxone 250 mg IM vs spectinomycin 2 g IM vs amoxicillin 3 g orally
Kirkcaldy 2014[52]	Dual	Gentamicin 240 mg IM + azithromycin 2 g orally vs gemifloxacin 320 mg orally + azithromycin 2 g orally
Ramus 2001[53]	Single	Ceftriaxone 125 mg IM vs cefixime 400 g orally
Ross 2017[54]	Dual	Gentamicin 240 mg IM + azithromycin 1 g orally vs ceftriaxone 500 mg IM + azithromycin 1 g orally
Taylor 2016[55]	Single	ETX0914 2000 mg orally vs ETX0914 3000 mg orally vs ceftriaxone 500 mg IM
Yuan 2016[56]	Dual vs single	Ceftriaxone 250 mg IM + azithromycin 1 g orally vs fosfomycin trometamol 3 g orally on days 1, 3 and 5

2.6.2 Quality appraisal

Critical appraisal of each study was performed by a single researcher, and quality assured by a second researcher.

The quality appraisal of RCTs for therapeutic interventions was performed using the "Cochrane Collaboration's tool for assessing risk of bias"[57] (see Appendix 6.1.3.). For each criterion the definitions described in the Cochrane Handbook were used. If applicable, risk of bias for the items regarding detection bias and attrition bias were assessed per class of outcomes (e.g. subjective and objective outcomes). In the end, each study was labelled as low risk of bias, or high risk of bias according to the criteria described in the Cochrane Handbook.

2.7 Additional literature search: diagnostic tests for syphilis

In consensus with the GDG, the following tests were included:

- Tests that detect syphilis in biological specimen, PCR and test kits included.
- Strategies of different test sequences and comparison of strategies with each other.
- Not included were the laboratory detection methods for the visual demonstration of *T. pallidum* and tests used for confirming or excluding neurosyphilis, cardiovascular syphilis, ocular syphilis and auricular syphilis.

2.7.1 Search strategy

On 26/03/2018 a search was performed to identify systematic reviews, randomised controlled trials, and observational studies comparing diagnostic tests to reference standard tests or screening strategies in symptomatic or asymptomatic sexually active men and women including adolescents aged 15 years and older. MEDLINE (including PreMedline), CENTRAL and the Cochrane Database of Systematic Reviews, the Cochrane Library Health Technology Assessment Database, and the Database of Abstracts of Reviews of Effects were searched.

In MEDLINE and Cochrane databases 87 potential relevant references were identified. After de-duplication 84 references remained. Based on title and abstract 67 studies were excluded. Of the remaining 17 studies, alongside an additional 25 studies that were identified through Cantor 2016 guideline and other sources there were 42 full text articles (2 systematic reviews and 40 primary studies) assessed for eligibility.

Systematic reviews: Of the 2 remaining reviews, both were excluded with reason (Appendix 2.4.4).

Primary studies: Of the 40 remaining primary studies, 10 studies were included and 30 were excluded with reason (Appendix 2.4.4).

Table 10 – Diagnostic tests for syphilis - Included observational studies

Reference	Interventions
Binnicker 2012[58]	Reverse screening vs traditional screening algorithm
Castro 2010[59]	Chembio Dual Path Platform (DPP) syphilis screen and confirm assay
Hess 2014[60]	Chembio DPP syphilis screen and confirm assay Chembio DPP HIV-HCV-syphilis assay Chembio DPP HIV-syphilis assay
Holden 2018[61]	SD Bioline HIV-syphilis duo test
Kalou 2016[62]	Chembio DPP HIV-syphilis assay
Leslie 2007[63]	TaqMan real-time polymerase chain reaction (PCR) assay (TpPCR)
Mishra 2011[64]	Reverse screening vs traditional screening algorithm
Tsang 2007[65]	Trep-Check IgG enzyme immunoassay (EIA)
Wong 2011[66]	Trep-Sure EIA
Zorzi 2017[67]	SD Bioline Syphilis 3.0 assay Chembio DPP syphilis screen and confirm

2.7.2 *Quality appraisal*

Critical appraisal of each primary study was performed by a single researcher, and quality assured by a second researcher. Retrieved diagnostic studies were assessed for the risk of bias by means of the QUADAS-2 tool. The four domains assessed for risk of bias were patient selection, index test, reference standard, and flow and timing. Applicability concerns were assessed in the first three domains. In each domain, we answered the signalling questions with 'Yes', 'No', or 'Unclear' and for each domain judged the risk of bias as 'Low', 'High', or 'Unclear' risk. The overall quality of evidence was summarised using GRADE methodology recommended for diagnostic tests.[49]

The tools used for the quality appraisal as the results of the quality appraisal are presented in the Appendix 6.1.2. The results of the quality appraisal are presented in the Appendix 6.1.2. (Table 12). The GRADE rating was applied to the 10 selected primary studies. For the diagnostic- strategy studies; one was of moderate and one of low quality with serious to very serious risk of bias. The remaining 8 studies were of low to very low quality with a serious to very serious risk of bias.

2.8 Additional literature search: treatment for syphilis

2.8.1 *Treatment for syphilis in primary care*

2.8.1.1 *Search strategy*

On 19/04/2018 a search was performed to identify systematic reviews and primary studies comparing treatment of syphilis in men and women including young people.

The following databases were included in the literature search:

- The Cochrane Database of systematic reviews (http://www.cochrane.org)
- Medline (http://www.ncbi.nlm.nih.gov/pubmed)
- Embase (http://www.embase.com/)
- PubMed database (https://www.ncbi.nlm.nih.gov/pubmed/)

The electronic search for systematic reviews, meta-analyses and guidelines covered the period from **01/03/2013 to 19/04/2018.**

Further information about ongoing research was obtained by contacting study authors and organisations. The EMA website was consulted to find all information about the authorization for medicines. Members of the GDG were also consulted to identify relevant evidence that might have been missed during the search process.

A combination of appropriate MeSH terms and free text words was used (Appendix 2.5). The PICOs and the search strategy corresponding to our research questions are documented in 2.3.2 and Appendix 2.5.

- Pathology: **Syphilis OR Treponema pallidum OR treponemal infections;**

- Field of search (intervention): **treatment**, according to the research questions.
- Type of reference (study design) included: **(systematic) reviews OR meta-analyses OR guidelines OR RCT's OR controlled clinical trials**

Studies were screened on **title and abstract** by two researchers (Clare Jones and Mark Perry) with the PICO in- and exclusion criteria. In case of doubt the content experts were consulted. First, the titles and abstracts of the identified studies were checked and irrelevant studies were eliminated. In a second step, the remaining papers were screened by reading their **full-text**. If no full-text was available, the study was excluded for the final recommendations. Reference lists of the selected studies were reviewed for additional relevant manuscripts.

The screening of the **guidelines** was performed on title and abstract by two researchers (Clare Jones and Mark Perry) based on the PICO in- and exclusion criteria.

2.8.1.2 Selection of systematic reviews and primary studies

The CDC Guideline[10] for the management of adult syphilis identified 2 systematic reviews[3; 4;6] and 1 RCT[14] that were ordered for this question. The RCT[14] was included. One Cochrane systematic review[68, 69] was included for information and the 3 included RCTs checked. One RCT[70] was already ordered from the CDC guideline and included. The other 2 RCTs were ordered and included.[71,72]

The other systematic review[73] was excluded due to study design not matching the review protocol. The studies from the review were checked and 2 relevant RCTs[74, 75] were ordered and included in this report.

Reasons for excluded studies are listed in the excluded studies list in Appendix 2.5.5.

4 RCTs[76-79] were identified in the search that met the protocol and were included.

In total, 18 RCTs and observational studies were included in this review:

- 9 RCTs; 5 RCTs[14,71, 72, 74, 75{] from the CDC guideline and 4 RCTs[76-79] from the search.
- 9 observational studies of which 7 [80-87] were identified from the search, 1 study from the CDC guideline[88] and 1 study[81] was retrieved from a systematic review[89].

Table 11 – Treatment for syphilis - Included primary studies

Reference	Treatment	Interventions
Andrade 2017[76]	Single vs single	Benzathine Penicillin G 2.4 million units IM injection three times over 3 weeks ***versus*** Benzathine Penicillin G 2.4 million units IM injection once
Cao 2017[77]	Single vs single	Benzathine Penicillin G 2.4 million units IM injection, once weekly for two weeks ***versus*** Ceftriaxone 1.0 intravenously, once daily for 10 days
Costa-silva 2016[80]	Single vs single	Benzathine Penicillin G 2.4 ***versus*** three weekly doses of Benzathine Penicillin G (dose not reported)
Drago 2016[78]	Triple vs single	Benzathine Penicillin G 2.4 million units by IM injection (one dose for people with primary, secondary and early latent syphilis, but 3 doses over 3 weeks for people with late latent syphilis) PLUS Ceftriaxone 1g by IM injection daily for 10 days followed by oral doxycycline 100mg twice daily for 20 days ***versus*** Benzathine Penicillin G 2.4 million units injection (one dose for people with primary, secondary and early latent syphilis, but 3 doses over 3 weeks for people with late latent syphilis)

Ghanem 2006[81]	Single vs single	Benzathine Penicillin G 2.4 million units IM as single dose ***versus*** doxycycline100 mg orally, twice daily for 14 days
Hook 2002[71]	Single vs single vs single	Azithromycin 2g single oral dose ***versus*** Azithromycin 4g, given by 2x2g doses ***versus*** Penicillin G Benzathine 2.4 million units IM injection in one site or 4.8 million units (two IM injections of 2.4 million units given 7 days apart) in the other site where this was standard practice at the time of the study
Hook 2010[70]	Single vs single	Azithromycin 2g single oral dose ***versus*** Benzathine Penicillin G 2.4 million units IM (2 injections of 1.2 million units)
Liu 2017[89]	Single vs single	Ceftriaxone, intravenous infusion of 10 g once daily for ten days ***versus*** Penicillin G procaine as IM injection of 800,000 units once daily for 15 days
Riedner 2005[72]	Single vs single	Azithromycin 2 g orally ***versus*** Penicillin G Benzathine 2.4 million units IM
Rolfs 1997[74]	Triple vs single	Penicillin G Benzathine 2.4 million units by IM injection (plus 2g amoxicillin and 500mg probenecid) ***versus*** Penicillin G Benzathine 2.4 million units by IM injection (plus placebo)
Salado 2016[82]	Single vs single	Doxycycline 100 mg orally twice daily for 14 days for early syphilis (primary, secondary and early latent stages) and for 30 days for late latent syphilis ***versus*** benzathine penicillin G, a single dose of IM 2.4 million units for early syphilis and 3 doses each at 1-week intervals for late latent syphilis. At the beginning of the study period 15 patients were treated with I procaine penicillin (1 dose of 600,000 units once daily for ten days) these cases were grouped with the Benzathine Penicillin G (BPG) treated cases
Shao 2016[83]	Single vs single vs single	Minocycline 2 weeks, 100 mg orally, twice daily, for 14 days ***versus*** minocycline 4 weeks, 100 mg orally, twice daily, for 28 days ***versus*** benzathine penicillin G as a single IM dose of 2.4 million units
Smith 2004[75]	Single vs dual	Ceftriaxone 1g IM injection daily for 15 days ***versus*** Procaine penicillin 2.4 million units by IM daily injection plus probenecid 500mg by mouth for 15 days
Tsai 2014[84]	Single vs single	Doxycycline as 100 mg twice daily for 14 days ***versus*** benzathine penicillin G as a single dose of 2.4 million units
Wong 2008[88]	Single vs single/single	Benzathine Penicillin G 2.4 million units in a single dose intramuscularly ***versus*** doxycycline 100 mg orally, twice daily for 14 days or tetracycline 500 mg orally, 4 times daily for 14 days.
Xiao 2017[85]	Single vs single	Doxycycline 100 mg orally twice daily for 14 days ***versus*** benzathine penicillin G 2.4 million units IM single dose
Yang 2014[86]	Single vs single	Penicillin G Benzathine single dose (2.4 million units, 1179 IU/mg) IM ***versus*** Penicillin G Benzathine triple dose (2.4 million units, 1179 IU/mg) IM
Yang 2016[87]	Triple vs single	Single-dose benzathine Penicillin G (2.4 million units) ***versus*** azithromycin 2g

2.8.2 *Quality appraisal*

Critical appraisal of each study was performed by a single researcher, and quality assured by a second researcher.

The quality appraisal of RCTs for therapeutic interventions was performed using the "Cochrane Collaboration's tool for assessing risk of bias".[90] For each criterion the definitions as described in the Cochrane Handbook were used. If applicable, risk of bias for the items regarding detection bias and attrition bias were assessed per class of outcomes (e.g. subjective and objective outcomes). In the end, each study was labelled as low risk of bias or high risk of bias according to the criteria described in the Cochrane Handbook. For the assessment of the quality of comparative observational studies the Cochrane Collaboration's tool for assessing risk of bias was also used.

Study limitations in observational studies were evaluated using GRADE criteria: failure to develop and apply appropriate eligibility criteria (inclusion of control population); under- or overmatching in case-control studies; selection of exposed and unexposed in cohort studies from different populations; flawed measurement of both exposure and outcome; differences in measurement of exposure (e.g., recall bias in case-control studies); differential surveillance for outcome in exposed and unexposed in cohort studies; failure to adequately control confounding; failure of accurate measurement of all known prognostic factors; failure to match for prognostic factors and/or lack of adjustment in statistical analysis, and incomplete follow-up.

The tools used for the quality appraisal and the results of the quality appraisal are presented in Appendix 6.1.3.

2.9 Data extraction

Data extraction was performed by one researcher and quality assured by a second researcher. Data were entered in evidence tables using standard KCE templates. All evidence tables are reported in Appendix 7.

2.10 Statistical analyses

For diagnostic test accuracy studies, if sufficient data were available meta-analyses were performed according to the statistical guidelines described in the Cochrane Handbook, (http://srdta.cochrane.org/handbook-dta-reviews). However, in the case of the review for the diagnostic accuracy of gonorrhoea, meta-analyses were not possible. Where meta-analyses were not possible or when data were not presented in sufficient detail to enable statistical pooling, data were presented as ranges of summary statistics. Coupled forest plots of sensitivity and specificity with their 95% CI across studies (at various thresholds) were produced for each test. In order to do this, 2×2 tables (the number of true positives, false positives, true negatives and false negatives) were directly taken from the study if given, or else were derived from raw data or calculated from the set of test accuracy statistics.

For intervention studies, separate analyses were done for each comparison (intervention vs. comparator). Heterogeneity was statistically assessed using $\chi 2$ test and I^2 statistic. If heterogeneity was present, a random-effects model was used instead of a fixed-effect model. Possible reasons for heterogeneity were explored post-hoc. Sensitivity analysis was performed by removing outliers from the analysis. Studies that were clinically heterogeneous or did not present the data in sufficient detail to enable statistical pooling were summarized qualitatively. For binary variables where there were zero events in either arm or a less than 1% event rate, Peto odds ratios, rather than risk ratios, were calculated. Peto odds ratios are more appropriate for data with a low number of events. Absolute measures were calculated using the risk difference. Imprecision was measured using default

For therapeutic interventions for syphilis, data from RCTs and observational studies were analysed separately. Imprecision was measured using sample size where very serious imprecision was suggested for a sample size of less than 70, serious imprecision for sample sizes from 70-350 and no imprecision when the sample size was over 350 participants. In one study[71] with 3 arms (azithromycin 2g vs azithromycin 3g vs BPG) comparisons were made between the two doses of azithromycin and between BPG compared to azithromycin (both doses combined). In one study[83] with 3 arms (minocycline 2 weeks vs minocycline 4 weeks vs BPG) comparisons were made between the two doses of minocycline and between BPG compared to minocycline (both doses combined).

Forest plots are reported in Appendix 8.

2.11 Grading evidence

For each recommendation, we provided its strength and the quality of the supporting evidence.[91] According to GRADE, we classified the quality of evidence into 4 categories: high, moderate, low, and very low (Table 12 and Table 13). The quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect was adequate to support a particular recommendation.

GRADE for guidelines was used, meaning that the evidence across all outcomes and across studies for a particular recommendation was assessed. The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

For RCTs, quality rating was initially considered to be of high level (Table 12). The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 points respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain.[92]

Observational studies were by default considered low level of evidence (Table 12 and Table 13). However, the level of evidence of observational studies with no threats to validity can be upgraded for a number of reasons:

1. Large magnitude of effects: The larger the magnitude of effect, the stronger becomes the evidence. As a rule of thumb, the following criteria were proposed by GRADE:
   a. Large, i.e. risk ratio (RR) >2 or <0.5 (based on consistent evidence from at least 2 studies, with no plausible confounders): upgrade 1 level
   b. Very large, i.e. RR >5 or <0.2 (based on direct evidence with no major threats to validity): upgrade 2 levels
2. All plausible confounders: all plausible confounding from observational studies or randomized trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed
3. Dose-response gradient: The presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence.

The general principles used to downgrade the quality rating are summarized in Table 14.

Table 12 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.

Table 13 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

Table 14 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of invalidated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down.
Indirectness	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision	Evaluation of the imprecision of results was primarily based on examination of the 95%CI. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention. Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

For diagnosis of gonorrhoea, Summary of Findings tables were set up, using sensitivity and specificity as critical outcomes. The GRADE profiles were provided by gender, sample site and assay (see Appendix 9, Table 25). Of note, although this guideline did not cover chlamydia, the GDG requested the results of the combi NAAT, as the TMA Aptima Combo test is commonly used in Belgium, to be reported. The evidence is summarised in Table 26 in the Appendix 9.

For treatment of gonorrhoea, Summary of Findings tables were set up, focusing on critical and important outcomes. GRADE was applied to obtain a level of quality evidence from high to very low for each outcome (Appendix 9, Table 27 to Table 32).

For diagnosis of syphilis, Summary of Findings tables were set up, using sensitivity and specificity as critical outcomes. The GRADE profiles were provided by type of tests (e.g. PCR, EIA, Chembio DPP) and gender, by screening tests (treponemal and/or non-treponemal tests) and samples used (serum sample, plasma or blood sample) and finally, by strategy (e.g. traditional algorithm, reverse algorithm) (see Appendix 9 Table 33 and Table 34).

For treatment of syphilis, Summary of Findings tables were set up, focusing on critical and important outcomes. GRADE was applied to obtain a level of quality evidence from high to very low for each outcome (Appendix 9, Table 35 to Table 46).

2.12 Formulation of recommendations

The evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to guide the development of clinical practice recommendations (from very low quality to high quality) and presented to the GDG, who formulated recommendations for clinical practice based on the evidence. In some cases, the GDG members added recommendations that are really important for practitioners but are not appropriate for formal ratings of quality of evidence according to the GRADE approach: 'Good practice statements' in blue tables. Good practice statements typically represent situations in which a large and compelling body of indirect evidence, made up of linked evidence including several indirect comparisons, strongly support the net benefit of the recommended action.[93] The same strategy was followed by WHO.[22]

The recommendations for the diagnosis and management of gonorrhoea, syphilis and chlamydia (section 2 of the guidelines) were separately discussed. The retrieved evidence is presented in the respective chapters. For each chapter, the evidence and a first draft of recommendations was prepared by NGC and KCE and discussed at the GDG meetings.

Based on the retrieved evidence, the first draft of recommendations was prepared by a small working group (KCE experts and NGC). This first draft was, together with the evidence tables, circulated to the guideline development group one to two weeks prior to the face-to-face meetings (30/3/2018, 08/06/2018, 06/09/2018, 10/09/2018, 04/10/2018, 22/10/2018 and 07/11/2018). Recommendations were changed if important new evidence supported this change. Based on the discussion meetings a second draft of recommendations was prepared and the summary table once more circulated to the guideline development group. GDG members stated in the table if they agreed 'Yes' or 'No' and added comments whenever they disagreed. These comments were discussed at the next GDG meeting before a final approval and consensus was reached.

The strength of each recommendation was assigned using the GRADE system (Table 15). The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), quality of available evidence, values and preferences, and estimated cost (resource utilization). For this guideline, no formal cost-effectiveness study was conducted. Factors that influence the strength of a recommendation are reported in Table 16.

Table 15 – Strength of recommendations according to the GRADE system

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice)*
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice)*

Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

Table 16 – Factors that influence the strength of a recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention, i.e. the greater the resources consumed, the lower the likelihood that a strong recommendation is warranted

Sources: Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A et al. An Official ATS Statement: Grading the Quality of Evidence and Strength of Recommendations in ATS Guidelines and Recommendations. Am J Respir Crit Care Med 2006; 174:605–14.
Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B et al. Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines - Report From an American College of Chest Physicians Task Force. Chest 2006; 129:174-81.

A strong recommendation implies that most patients would want the recommended course of action. A weak recommendation implies that the majority of informed patients would want the intervention, but many would not.[94, 95] Specifically, a strong negative recommendation means the harms of the recommended approach clearly exceed the benefits whereas a weak negative recommendation implies that the majority of patients would not want the intervention, but many would. In the case of a weak recommendation, clinicians are especially required to spend adequate time with patients to discuss patients' values and preferences. Such an in-depth discussion is necessary for the patient to make an informed decision. This may lead a significant proportion of patients to choose an alternative approach. Fully informed patients are in the best position to make decisions that are consistent with the best evidence and patients' values and preferences.

For policy-makers, a strong recommendation implies that variability in clinical practice between individuals or regions would likely be inappropriate whereas a weak recommendation implies that variability between individuals or regions may be appropriate, and use as a quality of care criterion is inappropriate.[94, 95]

We offer the suggested interpretation of "strong" and "weak" recommendations in Table 17.

Table 17 – Interpretation of strong and conditional (weak)* recommendations

Implications	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

** the terms ''conditional'' and ''weak'' can be used synonymously*
Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

2.13 External review

The recommendations prepared by the guideline development group were circulated to sexual health associations involved in research, to citizens, patients and professionals working in sexual health, STI, and other modalities of STI prevention, screening, diagnosis and treatment (Table 18). Each association was asked to assign one or two key representatives to act as external reviewers of the draft guideline. All expert referees made declarations of interest.

Table 18 – List of invited Professional Associations and Patients Organisations

- Alias vzw (association that supports male sex workers)
- Boysproject Antwerpen
- Cercle Homosexuel Etudiant (CHEN) & CHEFF (Federation of 7 CHEN)
- Centrum Algemeen Welzijnswerk (CAW) Antwerpen
- Belgian HIV Reference Centers and BREACH Foundation
- Domus Medica (represents the interests of GPs and general practitioner circles in Flanders)
- Dokters van de Wereld
- Espace P asbl (association that supports sex workers)
- Exaequo (health promotion association for MSM)
- Fédération Laïque de Centres de Planning Familial (FLCPF) (support structure for family planning centres)

- Fédération des Centres de Planning Familial (FPS) (family planning centres)
- Fédération des Maisons médicales et des collectifs de santé francophones
- Gezondheidszorg en hulpverlening aan prostituees (Ghapro offers health care and assistance to sex workers)
- Pasop vzw (Pasop offers health care and assistance to sex workers)
- Planning Marolles & Centre de Planning Familial de Uccle (family planning centres)
- Plannings Aimer (l'Université libre de Bruxelles) (family planning centres)
- Plateforme Migr'en santé Charleroi - Mons
- Plate-Forme Prévention Sida (association working on the prevention of HIV-AIDS and other STIs)
- Sensoa (Flemish expertise centre for sexual health)
- Service de Santé Affective, Sexuelle et de Réduction des Risques (SASER), Namur
- Sida Sol (association aims at the primary, secondary and tertiary prevention of AIDS and other STIs)
- SIDA'SOS (association dedicated to young people and active in the fields of health education and promotion)
- Société Scientifique de Médecine Générale (SSMG represents French-speaking general practitioners in Belgium)
- Vakgroep eerstelijns- en Interdisciplinaire Zorg, Universiteit Antwerpen
- Vlaamse Beroepsorganisatie van Vroedvrouwen (VBOV, Flemish Professional Organisation of Midwives)

Globally, 24 external experts and 21 stakeholders were involved in the evaluation of the clinical recommendations. All invited panellists received the scientific reports for all research questions and were asked to score each recommendation on a 5-point Likert scale indicating their level of agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' 'somewhat disagree', '3' 'unsure', '4' 'somewhat agree', and '5' 'completely agree' (the panellists were also able to answer 'not applicable' if they were not familiar with the underlying evidence). If panellists disagreed with the recommendation (score '1' or '2'), they were asked to provide an explanation supported by appropriate evidence. Scientific arguments reported by these experts were used to adapt the formulation or the strength of the clinical recommendations. A summary table was made of the scores showing that the score was 4 to 5 for 89% of the recommendations. The comments were summarised and presented to the stakeholders at the meeting. Some minor changes were made to the recommendations accordingly (textual clarification rather than content changes). For example, under 'Diagnostic tests for gonorrhoea in men', one of the recommendation was 'use a urethral or first flow urine sample for a combined gonorrhoea-chlamydia NAAT'. It was reformulated as follows 'use a first flow urine or a urethral sample for a combined gonorrhoea-chlamydia NAAT' to stress the preference on the first flow urine sample.

2.14 Final validation

As part of the standard KCE procedures, an external scientific validation of the report was conducted prior to its publication. This validation was done in two phases. First, the scientific content was assessed by two clinicians on January 29th 2019 (Henry de Vries; Charles Cazanave). Second, the methodology was validated making use of the AGREE II checklist. This validation process was chaired by CEBAM on February 5th 2019 (Dirk Ramaekers, Martine Goossens, Annelies Van Raemdonck).

3 CLINICAL RECOMMENDATIONS

The clinical recommendations for chlamydia testing, diagnosis and treatment will be available through the website of the 'Working group Development of primary Care Guidelines (http://www.ebpnet.be-guidelines.be/home) and the website from the Belgian Evidence Based Practice network (Ebpracticenet https://www.ebpnet.be/nl/Pages/default.aspx). The results are therefore not presented in this report.

3.1 Assessment of risk for gonorrhoea

Table 19 – Risk factors and risk groups for gonorrhoea infection: overview of international guidelines

Source	Recommendation for 1st line
US Preventive Services Task Force 2014[25] All sexually active adolescents and adults, including pregnant women	Risk factors: • Age: between 20 and 24 years • Having a new sex partner, more than 1 sex partner, a sex partner with concurrent partners, or a sex partner who has a STI; • Inconsistent condom use among persons who are not in mutually monogamous relationships; • Previous or coexisting STI; and exchanging sex for money or drugs.
British Association for Sexual Health and HIV 2011[96]	Risk groups: • MSM • Sex workers • Young people • Pregnant women • Known contacts of a gonorrhoea patient
CDC 2015[12]	Sexual behaviour other than being in a long-term mutually monogamous relationship with a partner known to be uninfected. Non-consistent and incorrect use of condoms. Other specific risk factors: • Persons seeking treatment or evaluation of an STI • HIV-serosorting practices • A chlamydia, gonorrhoea or syphilis infection in the past 3 months • Pregnant women < 25 years

	• Pregnant women ≥ 25 years with a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a STI; inconsistent condom use among persons not in mutually monogamous relationships, previous or coexisting STI, and exchanging sex for money or drugs. • MSM with multiple anonymous partners and abuse of substances
WHO guidelines for the treatment of *Neisseria gonorrhoeae* 2016[22]	Reference to the WHO Global strategy on STIs, 2016-2021: Each country needs to define the specific populations that are most affected by STI epidemics (key populations). • Most likely to have a high number of sex partners, such as sex workers and their clients. • Other populations for consideration include men who have sex with men, transgendered people, and people with an existing STI, including people living with HIV. • Many of these groups overlap with groups recognized as key populations for HIV. • Other groups considered to be particularly vulnerable to STIs include young people and adolescents, women, mobile populations, children and young people living on the street, prisoners, drug users and people affected by conflict and civil unrest.

3.2 Diagnosis of gonorrhoea

The diagnosis of uncomplicated gonorrhoea is established by identification of *N. gonorrhoea* in genital, rectal, or pharyngeal secretions with NAATs or culture and in symptomatic patients on urethral swabs by Gram stain microscopy.[2] NAATs are highly sensitive and specific diagnostic tests that can be conducted on a wide range of samples, including urine, vulvovaginal, cervical, rectal and urethral swabs. NAATs have a sensitivity of over 90%, which is higher than for culture. The sensitivity varies by NAAT type and is slightly lower for rectal and pharyngeal samples.

A drawback of currently available commercial NAATs is their inability to provide information on antimicrobial susceptibility. Cultures should be done in parallel with NAATs to allow for susceptibility testing. Optimal culture isolation of *N. gonorrhoea* requires good specimen collection, timely inoculation into adequate and appropriate culture media, proper transportation and appropriate incubation.[22]

Bedside Gram-stained smears can provide a presumptive diagnosis of gonorrhoea, especially among symptomatic men with urethritis.[22] Confirmation with NAAT is recommended except for low-income settings (not applicable for Belgium).

Chlamydia and gonorrhoea are the two most prevalent bacterial STIs. Since co-infections are common, combined diagnostic test platforms have been developed testing for both organisms on the same sample. The GDG asked to report the retrieved diagnostic characteristics on chlamydia for the *C. trachomatis* - *N. gonorrhoea* combination platform TMA Aptima Combo which is particularly of interest for Belgium.

3.2.1 Recommendations from international guidelines

Table 20 – Diagnosis recommendations for gonorrhoea from selected clinical guidelines

Source	Recommendation for 1st line	Remarks
Target population (see also section below which samples for specific groups)		
US Preventive Services Task Force 2014[25] All sexually active adolescents and adults, including pregnant women	The USPSTF recommends screening for gonorrhoea in sexually active females aged 24 years or younger and in older women who are at increased risk for infection (GRADE B – There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial).	Potential harms of screening for gonorrhoea include false-positive or false-negative results as well as labelling and anxiety associated with positive results.
US Preventive Services Task Force 2014[25] All sexually active adolescents and adults, including pregnant women	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for gonorrhoea in men (GRADE I - The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined).	
IUSTI 2012[2]	Indications for testing [IV; C] • Symptoms or signs of urethral discharge in men; • Vaginal discharge with risk factor for STI (age <30 years, new sexual partner); • Mucopurulent cervicitis; • Persons diagnosed with any other STI; • Sexual partner of persons with an STI or PID; • Acute epididymo-orchitis in a male aged ,40 years; • Acute PID; • When screening young adults (,25 years of age) for STI; • When screening individuals with new or multiple recent sexual partners; • Purulent conjunctivitis in a neonate or adult; • Mother of a newborn with ophthalmia neonatorum.	
Diagnostic tests		
US Preventive Services Task Force 2014[25] All sexually active adolescents and adults, including pregnant women	*N. gonorrhoeae* infection should be diagnosed by using NAATs: • Rectal and pharyngeal swabs can be collected from persons who engage in receptive anal intercourse and oral sex, although these collection sites have not been cleared by the FDA.	NAATs have high sensitivity and specificity and are cleared by the U.S. Food and Drug Administration (FDA) for use on urogenital sites, including male and female urine, as well as clinician-collected endocervical, vaginal, and male urethral

	• Urine testing with NAATs is at least as sensitive as testing with endocervical specimens, clinician- or self-collected vaginal specimens, or urethral specimens that are self-collected in clinical settings. • The same specimen can be used to test for chlamydia and gonorrhoea.	specimens. Most NAATs that are cleared for use on vaginal swabs are also cleared for use on self-collected vaginal specimens in clinical settings.
British Association for Sexual Health and HIV 2011[96]	• NAATs are the test of choice for testing asymptomatic individuals for urethral or endocervical infection with gonorrhoea (IIa; B). • NAATs are the test of choice for testing rectal and pharyngeal infection in MSM. • Microscopy of Gram-stained endocervical and urethral smears is not recommended for routine practice. • A culture should be taken in all cases of gonorrhoea diagnosed by NAAT's prior to antibiotics being given, if possible, so that susceptibility testing can be performed and resistant strains identified. • Mucosal sites associated with symptoms (discharge and/or pain) or signs (discharge and/or inflammation) should be tested for *N. gonorrhoea*.	Culture remains a sensitive test for clinicians taking genital specimens and is essential for patients with persisting symptoms or signs after treatment to exclude antimicrobial resistance. Microscopy of Gram-stained endocervical and urethral smears has low (40-60%) sensitivity in screening asymptomatic patients
IUSTI 2012[2]	• NAATs are recommended in both symptomatic and asymptomatic infections, for urine and urethral swab specimens from men and for clinician-taken or self-taken vulvovaginal and endocervical swabs from women (IVc; C). • If the used diagnostic NAAT does not display a PPV exceeding 90%, positive samples are recommended to be subjected to confirmatory testing, i.e. repeated with a NAAT targeting another sequence (III; B). • NAATs are the test of choice for screening for rectal and pharyngeal gonococcal infections. It is recommended that strict local evaluation is performed before introducing a NAAT to test rectal and pharyngeal samples. When used after evaluation, confirmatory testing is recommended, i.e. repeated with a NAAT targeting another sequence (IIb; B). • Culture is recommended for confirmatory identification (III; B).	NAATs are more sensitive than culture, offer testing on a wider range of specimen types and are less demanding in specimen quality, transportation and storage. The performance characteristics of different commercially available or in-house gonococcal NAATs differ substantially, particularly in regard to specificity.
Which samples for specific groups		
British Association for Sexual Health and HIV 2011[96]	• **MSM**: Tests should be taken from all sites (urethra, rectum, and oropharynx) potentially exposed to infection as directed by the sexual history (recommendation C).	• **MSM**: Rectal infection may be acquired by transmission from the oropharynx in the absence of penetrative anal intercourse.

	• **Sex workers**: Test all sites potentially exposed to infection as indicated by sexual history. • **'Young' patients**: Testing in post-pubertal young men and women follows that in adults. • **Pregnant women**: Screening tests as for heterosexual women. • **Women with history of hysterectomy**: A urethral swab for culture offers a better yield than high vaginal culture. • **Patients who are known contacts of gonorrhoea**: Test all sites potentially exposed to infection as indicated by the sexual history.	• **Sex workers**: A history of condom use should not deter testing at exposed sites. • **'Young' patients**: Young people may be intimidated by the prospect of invasive tests and may prefer non-invasive options when available, notably urine testing. • **Patients who are known contacts of gonorrhoea**: Microscopy may be worthwhile even if the patient is asymptomatic.
IUSTI 2012[2]	• **MSM**: Tests should be taken from the urethra/urine, rectum and pharynx as directed by sexual practices. • **Symptomatic men with urethral discharge**: Microscopy using Gram or methylene blue staining is recommended as a rapid diagnostic test. • **Asymptomatic men and in identifying endocervical or rectal infection**: microscopy cannot be recommended as a test of exclusion in these situations. • **Asymptomatic women** are commonly offered screening for gonorrhoea and chlamydial infection by a single vulvovaginal or endocervical test. Sampling rectal and pharyngeal sites should be considered when there is a history of direct exposure. • Culture is recommended for confirmatory identification.	
Testing Intervals		
British Association for Sexual Health and HIV 2011[96]	• The minimum time interval between exposure and when to test for gonorrhoea has not been determined. • Repeat testing should relate to risk rather than to a prescribed frequency. • There is no compelling evidence to support frequent checks in sex workers, who have almost universal condom use at work. • No general recommendation on the frequency of repeat testing in asymptomatic patients is suggested.	

3.2.2 *Additional literature search: Diagnosis of gonorrhoea*

In consensus with the GDG, the following tests were included:

- Tests that detect gonorrhoea in biological specimens from various anatomical sites (urine, endocervix, urethra, vagina, anus, pharynx), for example NAATs[1];
- Self-collected tests (e.g. auto tests and online tests);
- Combination tests for gonorrhoea and chlamydia.

We looked for systematic reviews, randomised controlled trials (test-and-treat) as well as observational studies that investigated the tests that detect gonorrhoea in biological specimens. No randomised controlled trials (test-and-treat) were retrieved in the search. Eighteen observational studies were included in this review.

The studies investigated NAAT including transcription mediated amplification (TMA), polymerase chain reaction (PCR) and strand displacement assay (SDA). Some studies reported diagnostic accuracy of culture to diagnose gonorrhoea.

The following interventions were excluded in consensus with the laboratory experts of the GDG: Abbots CT real-time porA assay, Binax NOW immunochromotographic assay, BIORad Dx assay, NG Biostar, LDQA targeting porA pseudomgene and microscopy.

It was also decided to exclude the glans and L-Pap test samples as these samples are not used in Belgium for the diagnosis of gonorrhoea.

In order to avoid confusion about the terminology of the tests, an overview of the different assay names and their corresponding terminology is presented in Table 21.

Table 21 – List of assay names

Assay name used in reference	Abbreviation used in the scientific report	Abbreviation used in the appendix
SDA BD ProbeTec (ET)	SDA	SDA BD Probetec
SDA Becton Dickinsons Qx Amplified Assay (is used on the Viper system)	SDAQx	SDA BD Qx
PCR Max assay	PCR	PCR Max
Roche amplicor	PCR	PCR Roche
PCR Roche Cobas 4800 CT/NG v2.0 test	PCR	PCR C4800
TMA Aptima Combo	TMA	TMA Combo
TMA Aptima NG	TMA	TMA NG
PCR Abbott Realtime CT/NG	PCR	PCR Abbott
Xpert CT/NG (PCR on the GeneXpert machine)	PCR	PCR Xpert
LCR : DNA probe amplification assay	LCR	LCR
PCR AmpliSens multiplex real-time	PCR	PCR Ampli

Note: CT/NG: Chlamydia trachomatis/Neisseria gonorrhoeae; DNA: deoxyribonucleic acid; LCR: ligase chain reaction; PCR: polymerase chain reaction; TMA: transcription-mediated assay; SDA: strand displacement assay

[1] NAAT methodology involves amplification of specific *N. gonorrhoea* DNA or RNA sequences by polymerase chain reaction (PCR), strand displacement assay (SDA), or transcription-mediated assay (TMA). Ligase chain reaction is no longer commercially available. NAAT tests are currently not approved by the US Food and Drug Administration for use in the rectum, pharynx, and conjunctivae.

3.2.2.1 *Diagnostic accuracy of tests for gonorrhoea in men and women (mixed population)*

The single study retrieved (Cosentino) reported only results on the diagnostic accuracy in rectal samples.

Diagnostic accuracy of tests for gonorrhoea using rectal samples

One study[32] was identified that tested rectal samples in men and women using SDA, TMA and culture. The participants were eligible for the trial if they reported at least one lifetime episode of receptive anal intercourse.

- The **SDA** had a sensitivity of 76% and a specificity of 100% [Moderate quality evidence].
- The **TMA** had a sensitivity and specificity of 100% [High quality evidence].
- No results were reported for **PCR**.
- The same study using **culture** had a sensitivity of 24% [Moderate quality evidence] and specificity of 100%.

This was the only study that reported men and women outcomes combined rather than separately.

Conclusions on the diagnostic accuracy of tests for gonorrhoea in women and men

In Table 22, an overview is presented on the retrieved diagnostic accuracy of NAATs and culture tests in women and men.

Table 22 – Overview of the diagnostic accuracy to detect gonorrhoea in men and women

MEN AND WOMEN	Rectal
SDA	Sens: 76% Spec: 100%
TMA	Sens: 100% Spec: 100%
PCR	/
Culture	Sens: 24% Spec: 100%

In the GRADE profiles (Table 23), an overview is presented of the number of studies per comparison, the quality assessment and the summary of findings. These considerations served as a basis for the formulation of the conclusions and the recommendations.

Table 23 – GRADE profiles: Diagnostic tests for gonorrhoea in men and women, by assay

Study characteristics			Quality Assessment					Summary of findings Range % (95% CI)		
No. of studies	Design	No.	Risk of bias	Inconsistency[1]	Indirectness	Imprecision[2]	Other considerations	Sensitivity (%)	Specificity (%)	Quality
NAAT tests										
Men and women – rectal samples - SDA (prevalence: 4.2%)										
1	Diagnostic cohort study	497	No serious risk of bias	Not applicable	No serious indirectness	Serious imprecision	None	76 (53-92)	100 (99-100)	MODERATE
Men and women – rectal samples - TMA (prevalence: 4.2%)										
1	Diagnostic cohort study	497	No serious risk of bias	Not applicable	No serious indirectness	No serious imprecision	None	100 (84-100)	100 (99-100)	HIGH
Culture test										
Men and women – rectal samples (prevalence: 4.2%)										
1	Diagnostic cohort study	497	No serious risk of bias	Not applicable	No serious indirectness	Serious imprecision	None	24 (8 -47)	100 (99-100)	MODERATE

[1] Inconsistency was assessed by inspection of the sensitivity (considered to be the primary measure for this review) using the point estimate of individual studies on the forest plots. The evidence was downgraded by 1 increment if the individual study comparisons varied across 2 areas [(for example, 50–90% and 90–100%)] and by 2 increments if the individual study comparisons varied across 3 areas [(for example, 0–50%, 50–90% and 90–100%)].

[2] Imprecision was based on the range of point estimates or, if only one study contributed to the evidence, the 95% CI around the single study. As a general rule a variation of 0–20% was considered precise, 20–40% serious imprecision, and >40% very serious imprecision. Imprecision was assessed on the primary outcome measure for decision-making.

3.2.2.2 Diagnostic accuracy of tests for gonorrhoea in men

Eleven studies were identified that reported the diagnostic accuracy of NAATs and culture tests in men.[31, 34, 35, 38-40, 42, 44, 45, 48, 97]

Of these, seven studies also reported the diagnostic accuracy of NAATs and culture tests to detect chlamydia in men.[34, 35, 38, 42, 44, 45, 48]

The results are presented per sample site (rectal, urethral, oropharyngeal, first catch urine and pooled sample). An overview of the diagnostic accuracy and its corresponding grading profiles are presented in Table 25 and in Appendix 8.1 and 9.1.

Diagnostic accuracy of tests for gonorrhoea using rectal samples

Three studies compared SDA, TMA and culture testing on rectal samples from MSM.[38, 39, 42]

- The **SDA** had sensitivities ranging from 67-93% and specificities from 99-100% [Very low quality evidence].

  In one study self-collected rectal samples were compared to clinician-collected samples and the self-collected samples had a higher sensitivity of 77% compared to 67% in the clinician-collected samples [Very low quality evidence].[38]

- The **TMA** had sensitivities ranging from 78-100% and specificities 99-100% [Very low quality evidence].

  One study found that the self-collected rectal samples had a higher sensitivity of 84% compared to 78% in the clinician-collected sample [Very low quality evidence].[38]

- No studies were retrieved on **PCR** testing.

- Two studies tested the rectal samples for gonorrhoea using **cultures** from MSM and had considerably lower sensitivities of 35% and 49% whilst specificities were 100% for both [Low quality evidence].[38, 42]

Diagnostic accuracy of tests for gonorrhoea using urethral samples

Four studies were identified that reported sensitivities ranging from 99-100% and specificities from 97-100% when using urethral samples and TMA and SDA tests.[31, 34, 45, 97] No more details could be found on the description of the participants (e.g. % of MSM within the sample of men).

- The **SDA** and SDAQx tests ranged from 99-100% sensitivity and 99-100% specificity [Low quality evidence].
- The **TMA** reported sensitivities from 81.8-100% and specificities from 97-100% [Low quality evidence].
- **PCR**: one study[34] reported a sensitivity of 99.2% and specificity of 99.3% for symptomatic patients and a sensitivity of 81.8% and specificity of 99.8% for asymptomatic patients [High quality evidence].
- No studies were retrieved on **culture tests**.

Diagnostic accuracy of tests for gonorrhoea using oropharyngeal samples

Two studies tested SDA, TMA and culture on clinician-collected pharynx samples from a MSM population.[39, 42]

- The sensitivity for **SDA** was 88% and the specificity 99% for one study.[42] The other study[39] reported sensitivity of 95% for SDA and specificity of 98% [Very low quality evidence].
- Quite similar results were found for **TMA**: whereas one study[42] found sensitivity of 88% and specificity of 98%, the other study[39] reported a higher sensitivity 95% and a specificity of 100% [Very low quality evidence].
- No studies were retrieved on **PCR**.
- One study[42] reported that a **culture** test on the pharynx sample provided a sensitivity of 55% and specificity of 100% [Very low quality evidence].

Diagnostic accuracy of tests for gonorrhoea using first catch urine samples

Seven studies using the TMA, PCR and SDA tests on first catch urine samples from men were identified.[31, 34, 35, 40, 47, 48, 98] The sensitivities and specificities of all these tests ranged from 97-100% and specificities from 99-100%. No more details could be found on the description of the participants (e.g. % of MSM within the sample of men)

- Three studies reported **SDA** and **SDAQx** and found sensitivities ranged from 94.9% to 100% and specificities ranged from 96-100% [Moderate quality evidence].
- Four studies reported **TMA** sensitivities ranged from 98-100% and specificities from 99% to 100% [Moderate quality evidence].
- The **PCR** reported sensitivities of 98-100% and specificities of 100% for all five studies [Moderate quality evidence].
- No studies were retrieved on **culture** tests.

Diagnostic accuracy of tests for gonorrhoea using pooled versus non-pooled tests

One study[44] using the TMA test on pooled (using pharyngeal, rectal and urethral/first-void samples) versus non-pooled samples was identified from a study from MSM. The sensitivity of the pooled ample was 89.9% and the non-pooled sample was 98.6%. Specificity was not reported [Moderate quality evidence].

Conclusions on the diagnostic accuracy of tests for gonorrhoea in men

In Table 24, an overview is presented on the retrieved diagnostic accuracy of NAATs and culture tests in men (including MSM).

Table 24 – Overview of the diagnostic accuracy to detect gonorrhoea in men

MEN	Rectal (in MSM)	Urethra (population not stated)	Pharynx (in MSM)	Urine (population not stated)	Pooled vs non-pooled (in MSM)
SDA	Sens: 67-93% Spec: 99-100% PPV: 91.4-100%	Sens: 99-100% Spec: 99-100% PPV: 98.2-98.6%	Sens: 88-95% Spec: 98-99% PPV: 82.6-84.0%	Sens: 95-100% Spec: 96-100% PPV: 95.0-97.0%	/
TMA	Sens: 78-100% Spec: 99-100% PPV: 84.7-100%	Sens: 82-100% Spec: 97-100% PPV: 85.4-98.6%	Sens: 88-95% Spec: 98-100% PPV: 71.6-95.0%	Sens: 98-100% Spec: 99-100% PPV: 95.8-100.0%	Sens: 89.9% vs 98.6% Spec: not reported
PCR	/	Sensitivity: Symptomatic: 99.2% (97.0-99.9%) Asymptomatic: 81.8% (48.2-99.7%) Specificity: Symptomatic: 99.3% (98.3-99.8%) Asymptomatic: 99.8% (99.1-100%)	/	Sens: 98-100% Spec: 100% PPV: 97.3-100.0%	/
Culture	Sens: 35-49% Spec: 100% PPV: 100.0%	/	Sens: 55% Spec: 100% PPV: 100.0%	/	/

In the GRADE profiles tabulated below (Table 25), an overview is presented of the number of studies per comparison, the quality assessment and the summary of findings. These considerations served as a basis for the formulation of the conclusions and the recommendations.

Table 25 – GRADE profiles: Diagnostic tests for gonorrhoea in men, by sample type and assay

Study characteristics			Quality Assessment					Summary of findings Range % (95% CI)		Quality
No. of studies	**Design**	**No.**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sensitivity (%)**	**Specificity (%)**	
NAAT tests										
Men – rectal samples – SDA (prevalence: 9.4%, 11.7% and 11.7%)										
3	Diagnostic cohort studies	2240	Serious risk of bias[2]	Serious inconsistency[3]	No serious indirectness	Serious imprecision[4]	None	67 (56-77) to 93 (77-99)	99 (98-100) to 100 (100-100)	VERY LOW
Men – rectal samples – TMA (prevalence: 9.4%, 11.7% and 11.7%)										
3	Diagnostic cohort studies	2240	Serious risk of bias[2]	Serious inconsistency[3]	No serious indirectness	Serious imprecision[4]	None	78 (68-87) to 100 (88-100)	99 (98-99) to 100 (100-100)	VERY LOW
Men – urethral samples - SDA (prevalence: 9.2% and 14.5%)										
2	Diagnostic cohort studies	2536	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	99 (95-100) to 100 (97-100)	99 (98-100) to 100 (99-100)	LOW
Men – urethral samples – TMA (prevalence: 9.2%, 13.9%, 14.5% and 16.7%)										
4	Diagnostic cohort studies	5676	Serious risk of bias[2]	Serious inconsistency[3]	No serious indirectness	No serious imprecision	None	81.8 (48.2- 97.7) to 100 (96-100)	97 (96-98) to 100 (99-100)	LOW
Men – urethral samples – PCR (prevalence: 16.7%)										
1	Diagnostic cohort study	1818	No serious risk of bias	Not applicable	No serious indirectness	No serious imprecision	None	Symptomatic: 99.2 (97.0-99.9) Asymptomatic: 81.8 (48.2-99.7)	Symptomatic: 99.3 (98.3-99.8) Asymptomatic: 99.8 (99.1-100)	HIGH
Men – pharynx samples – SDA (prevalence 8.1% and 8.1%)										
2	Diagnostic cohort studies	5447	Very serious risk of bias[1]	Serious inconsistency[3]	No serious indirectness	No serious imprecision	None	88 (78-95) to 95 (75-100)	98 (96-100) to 99 (98-99)	VERY LOW
Men – pharynx samples – TMA (prevalence 8.1% and 8.1%)										
2	Diagnostic cohort studies	5447	Very serious risk of bias[1]	Serious inconsistency[3]	No serious indirectness	No serious imprecision	None	88 (78-95) to 95 (75-100)	98 (97-99) to 100 (98-100)	VERY LOW
Men – first catch urine – SDA (prevalence: 9.2%, 14.5% and 16.7%)										
3	Diagnostic cohort studies	4354	Serious risk of bias[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	94.9 (91.3-97.3) to 100 (97-100)	95.7 (93.8-97.2) to 100 (99-100)	MODERATE

Men – first catch urine – TMA (prevalence: 9.2%, 13.9, 14.5% and 16.7%)										
4	Diagnostic cohort studies	5676	Serious risk of bias[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	97.9 (95.2-99.3) to 100 (97-100)	99 (98-100) to 100 (99-100)	MODERATE
Men – first catch urine – PCR (prevalence: 0.4%, 3.6%, 9.2%, 12.9% and 16.7%)										
5	Diagnostic cohort studies	7796	Serious risk of bias[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	98 (89-100) to 100 (95-100)	99.5 (98.5-99.9) to 100 (100-100)	MODERATE
Men – pooled versus non pooled samples (pharyngeal, urethral/urine and rectal) – TMA (prevalence 27%)										
1	Diagnostic cohort study	1064	Serious risk of bias[2]	Not applicable	No serious indirectness	No serious imprecision	None	Pooled: 89.9 (85.8-93.1)	Not reported	MODERATE
Culture test										
Men – rectal samples (prevalence: 9.4% and 11.7%)										
2	Diagnostic cohort studies	1992	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	35 (25-46) to 49 (37-60)	100 (100-100)	LOW
Men – pharynx samples (prevalence: 11.7%)										
1	Diagnostic cohort study	1110	Very serious risk of bias[1]	Not applicable	No serious indirectness	Serious imprecision[4]	None	55 (42-67)	100 (100-100)	VERY LOW

[1] Risk of bias was assessed using the QUADAS-2 checklist. If there was one criterion with a high risk of bias the study was considered to have a serious risk of bias. If there were two or more criteria with a high risk of bias the study was considered to have a very serious risk of bias. The evidence was downgraded by 2 increments if the majority of studies were rated at very high risk of bias

[2] Risk of bias was assessed using the QUADAS-2 checklist. If there was one criterion with a high risk of bias the study was considered to have a serious risk of bias. If there were two or more criteria with a high risk of bias the study was considered to have a very serious risk of bias. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias

[3] Inconsistency was assessed by inspection of the sensitivity (considered to be the primary measure for this review) using the point estimate of individual studies on the forest plots. The evidence was downgraded by 1 increment if the individual study comparisons varied across 2 areas [(for example, 50–90% and 90–100%)] and by 2 increments if the individual study comparisons varied across 3 areas [(for example, 0–50%, 50–90% and 90–100%)].

[4] Imprecision was based on the range of point estimates or, if only one study contributed to the evidence, the 95% CI around the single study. As a general rule a variation of 0–20% was considered precise, 20–40% serious imprecision, and >40% very serious imprecision. Imprecision was assessed on the primary outcome measure for decision-making.

Diagnostic accuracy of gonorrhoea combined tests with chlamydia in men

Four studies[34, 38, 42, 45] reported the diagnostic accuracy of TMA Aptima Combo tests to detect chlamydia in men, using rectal samples,[38, 42] urethral and urine samples,[34, 45] and pharyngeal samples.[42]

In the GRADE profiles tabulated below (Table 26), an overview is presented of the number of studies per comparison, the quality assessment and the summary of findings. These considerations served as a basis for the formulation of the conclusions and the recommendations.

Table 26 – GRADE profiles: Diagnostic tests for chlamydia in men, by sample type

Study characteristics			Quality Assessment					Summary of findings Range %(95% CI)		Quality
No. of studies	Design	No.	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (%)	Specificity (%)	
Men – rectal samples – TMA										
2	Diagnostic cohort studies	2017	Serious risk of bias[2]	Serious inconsistency[3]	No serious indirectness	Serious imprecision[4]	None	64 (52-76) to 100 (93-100)	99 (97-99) to 100 (99 -100)	VERY LOW
Men – urethral samples – TMA										
2	Diagnostic cohort studies	4607	Serious risk of bias[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	94 (89-98) Symptomatic: 98.4 (95.3-99.7) Asymptomatic: 91.2 (83.4-96.1)	99 (98-100) Symptomatic: 98.5 (97.2-99.3) Asymptomatic: 99.1 (98.0-99.7)	MODERATE
Men – pharynx samples – TMA										
1	Diagnostic cohort studies	1110	Very serious risk of bias[1]	Not applicable	No serious indirectness	Serious imprecision[4]	None	64 (31-89)	100 (100-100)	VERY LOW

Men – first catch urine – TMA										
2	Diagnostic cohort studies	4607	Serious risk of bias[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	97 (92-99) Symptomatic: 99.5 (97.0-100.0) Asymptomatic: 98.9 (94.0-100.0)	99 (98-100) Symptomatic: 99.4 (98.4-99.8) Asymptomatic: 99.5 (98.5-99.9)	MODERATE

3.2.2.3 Conclusions: Diagnostic accuracy of tests for gonorrhoea in men

Urine and urethra

- **The NAAT tests (TMA, PCR and SDA) have a high sensitivity (97% or more) when used with urethral or first-void urine samples from men to diagnose gonorrhoea.**
- **The TMA Combo test obtained high sensitivity when used with urethral or first-void urine samples from men to diagnose both *C. trachomatis* and *N. gonorrhoea*.**

Rectal

- **The NAAT sensitivities (67-100%) were considerably higher than the sensitivities from the cultures (35-49%) when used with rectal samples from men to diagnose gonorrhoea.**
- **PCR was not evaluated in rectal samples.**
- **TMA had a higher sensitivity compared to SDA when used with rectal samples from men to diagnose gonorrhoea.**
- **In MSM, tests using self-collected rectal samples had a higher sensitivity than tests using clinician-collected rectal samples.**

In MSM, the sensitivity of NAAT tests on pooled samples (pharyngeal, urine/urethra and rectal samples) was 89.9% versus 98.6% in non-pooled samples. When pharyngeal sample is excluded from the pooled, the sensitivity was higher (94%).

Oropharyngeal

- **The NAAT sensitivities (88-100%) were higher than the sensitivities from the cultures (55-100%) when used with clinician-collected oropharyngeal sample from men to diagnose gonorrhoea.**
- **PCR was not evaluated in oropharyngeal samples.**
- **TMA and SDA have similar sensitivities when used with oropharyngeal sample from men to diagnose gonorrhoea.**

In MSM, the sensitivity of NAAT test on pooled samples (pharyngeal, urine/urethra and rectal samples) was 89.9% versus 98.6% in non-pooled samples.

Men versus women

- **No clear conclusions can be drawn on differences between genders for the tests or sites with the exception of urine samples where higher sensitivities were obtained in men with a narrower range.**

3.2.2.4 *Conclusions: Clinical outcomes of tests for gonorrhoea in men*

- **No conclusion can be drawn for the preferred method of sample selection from a patient point of view as there was no evidence for this outcome in men.**
- **No conclusion can be drawn on harms as there was no evidence for this outcome.**

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Diagnostic clinical evidence: • The evidence shows a **higher diagnostic accuracy of NAATs** compared to culture tests. • No evidence was reported on **potential harms**. However, a potential risk for false positives and false negatives in tests with lower sensitivity and specificity should be kept in mind. Both urine and urethral samples are fine for NAATs. Culture of urine is less performant than culture of urethral samples. But urethral culture samples require more experience from the clinician. If not well performed, sensitivity will drop.
Quality of evidence	Update literature search: 11 diagnostic studies ranging from very low quality to high quality evidence. Differences in sensitivity can be explained by the testing procedure (swab collection, time to transportation and storage conditions) in clinical practice compared to research settings. For example, TMA sensitivity could be lower due to 'instability' of RNA during transport (used for extraction and RNA analysis).
Costs (resource allocation)	The total cost of NAAT gonorrhoea tests are reimbursed. The patient pays the basic laboratory fee only. Testing is not limited in frequency per year. Preliminary data on tests used in Belgian laboratories show that the majority of laboratories use NAAT. Laboratories do report culture but unfrequently (Source: Sciensano). It is not known how many laboratories use NAATs for extra-genital samples. Each lab should indeed validate the commercial test that they use in their settings to test if the test insert specifics are valid. This is especially the case for rectal and pharyngeal tests. A retesting protocol should be set up in case the laboratory validation shows that the test does not perform optimally. By adding a confirmation test targeting a different DNA gonorrhoea sequence the number of false positives can be reduced. Testing from multiple sites is expensive. Therefore, pooling of samples, thereby reducing the number of samples from 3 to 2 or even 1 may benefit the patient especially when testing is to be repeated every 3 to 6 months in individuals with high risk sexual behaviour. Pooling of the three samples on site (clinician) versus in the laboratory: Lab-pooling has the advantage that individual results (rectal, pharyngeal, and urethral) can still be accessed at a later stage. Standardisation will be higher with lab-pooling. Site-pooling will mean setting up and validation of a difficult laboratory procedure for the combination sample (either 3 swabs or urine and 2 swabs). Cost will vary according to laboratory validations, multiple or single extraction of DNA/RNA, sample material, and single or multiple tests paid by the patient.

	The pooling of an oropharyngeal, urine/urethral and rectal sample on site (clinician) or in the laboratory are both an area of research. Laboratory pooling has recently been tried in Belgium in MSM and although NAAT inhibition improved, the study was too small to draw firm conclusions.[99] Postal self-collected: is not performed in clinical practice. Currently, no limitations for gonorrhoea testing exist in Belgium. But the combination of NAAT and culture on the same prescription is not allowed. In practice often gonorrhoea and chlamydia are tested together on one sample with one test platform. The reimbursement for chlamydia is limited to a maximum of twice a year and only for young people below the age of 21 years or when the patient is symptomatic. The cost for the patient when not reimbursed for chlamydia is approximately 30€.
Patients values and preferences	Rectal sampling: Rectal self-collected sample is preferred by the patient but sample collection by the clinician has other advantages e.g. screening for anal cancer. Therefore, both rectal sampling methods can be considered. Urethral versus urine samples*:* Men prefer urine sample and both men and clinicians have an aversion for urethral swab taking as it is painful*.*

Table 27 – Cost of diagnostic tests for gonorrhoea and chlamydia

	Nomenclature code	Test	Reimbursement interval if applicable	Full Cost in euros*	Reimbursement in euros*	Out-of-pocket in euros*
Any infectious disease	550395- 550406[a]	aerobic culture of vaginal or urethral sample, or sperm[b]		10.94	2.73	0.0
Chlamydia	550255-550266[a]	chlamydia molecular amplification[bc]	twice each calendar year for age-group <20 years and clear clinical signs of chlamydia infection	31.25	7.81	0.0
	550675-550686[a]	culture chlamydia[bc]	twice each calendar year for age-group <20 years and clear clinical signs of chlamydia infection	18.75	4.69	0.0
Gonorrhoea	550911-550922[a]	gonorrhoea molecular amplification[e]		12.5	3.13	0.0
	549312-549323[a]	aerobic culture of urine[e]		6.25	1.56	0.0

*Note. * no difference between ambulatory/hospitalisation, nor between patients with/without preferential reimbursement; [a]Maximum number ONCE for one clinical session; [b]No cumulation; [c]Specification of reimbursement indication on the prescription; [d] ONLY for non-urogenital infections, LGV or perihepatitis; max 5 numbers (551176 - 551180, 551972 - 551983, 551213 - 551224, 551891 - 551902) (rickettsiae, mycoplasma, chlamydia), maximum three per session, and no cumulation with 552016 antibodies for infectious organisms. [e] No cumulation*

3.2.2.5 Diagnostic accuracy of tests for gonorrhoea in women

Twelve studies were identified that reported the diagnostic accuracy of NAATs and culture tests in women.[33-37, 40, 41, 43, 46-48, 97] The results are presented per sample site (vulvovaginal, endocervical, vaginal, and first catch urine). An overview of the diagnostic accuracy and the corresponding grading profiles are presented in Appendix 8.1 and 9.1.

Diagnostic accuracy of tests for gonorrhoea using vulvovaginal samples (self-collected)

One study[43] reported that the **TMA** test with vulvovaginal samples gave a sensitivity of 99% and specificity of 100% [High quality evidence]. No studies were retrieved on SDA, PCR or culture tests [High quality evidence].

Diagnostic accuracy of tests for gonorrhoea using endocervical samples

Eight studies[33-35, 37, 43, 46-48] were identified that used endocervical samples to test with NAATs and culture.

- The **SDA** and SDAQx tests were reported in four studies.[33, 34, 46, 47] The sensitivities ranged from 88-98% and specificities from 99-100% [Low quality evidence].
- The **TMA** test was reported in five studies;[34, 37, 43, 46, 47] with sensitivities ranging from 91% to 100% and specificities from 99%-100% [High quality evidence].
- **PCR** testing was found in four studies.[34, 35, 46, 48] The sensitivities ranged from 87%-100% and specificities were 100% for all endocervical samples [Moderate quality evidence].
- **LCR** testing was reported in one study[11] with a sensitivity 96% and specificity of 100%. [Moderate quality evidence].
- Two studies used the endocervical sample to test the accuracy of **culture**. One study[37] had a sensitivity of 86% and specificity of 100% while the other study[43] reported 81% and 100% respectively (low risk of bias) [High quality evidence].

Diagnostic accuracy of tests for gonorrhoea using clinician-collected vaginal samples

Three studies were identified that used clinician-collected vaginal samples to diagnose gonorrhoea with two different NAAT tests.[34, 41, 48]

NAAT tests.

- Two studies[34, 41] used the **TMA** test and reported sensitivities of 94%-96%. One of the studies[41] reported results for the TMA Combo and TMA NG. [Moderate quality evidence].
- Two studies[34, 48] used the **PCR** test and reported sensitivities ranging from 95-97% and specificities of 99-100% [High quality evidence].

Diagnostic accuracy of tests for gonorrhoea using self-collected vaginal samples

Five studies were identified that used self-collected vaginal samples to diagnose gonorrhoea with NAAT tests.[33-35, 41, 47]

- Two studies[33, 47] used the **SDA** and SDA Qx test and reported sensitivity of 100% and specificity of 99% in both [Low quality evidence].
- Two studies[34, 35] used the **PCR** test and reported a sensitivity of 96% and 100% and specificity of 100% in both [Moderate quality evidence].
- One study[41] used the TMA Combo and TMA NG tests and found sensitivities of 99% and 96% and specificities of 100% and 96% respectively [Low quality evidence].
- No studies were retrieved on **culture** tests.

Diagnostic accuracy of tests for gonorrhoea using self-collected vaginal samples – posted to laboratory

One study[36] was identified that used self-collected vaginal samples that were posted to the laboratory with 3 NAAT tests to diagnose gonorrhoea.

- The **SDA** showed a sensitivity of 80% and a specificity of 100% [Very low quality evidence].
- The **TMA** had a sensitivity of 100% and a specificity of 100% [Very low quality evidence].
- **PCR** tests had a sensitivity of 100% and a specificity of 99% [Very low quality evidence].
- No studies were retrieved on **culture** tests.

Diagnostic accuracy of tests for gonorrhoea using first catch urine samples

Seven studies were identified that used first catch urine samples from women to detect gonorrhoea using SDA, PCR and TMA tests.[33-35, 40, 46, 48, 97]

- Four studies used the **SDA** and SDAQx test (one study reported results for both types of test) and reported sensitivities ranging from 77-98% and 96-100% specificity. The final study reported sensitivities of 77% and 86% and specificities of 96% and 97% for symptomatic and asymptomatic patients respectively [Very low quality evidence].
- Three studies[34, 46, 97] used the **TMA** test and sensitivities ranged from 83-97% and specificities from 99-100% [Moderate quality evidence].
- Five studies reported on the **PCR** test with four studies reporting sensitivities ranging from 87-100% and all had a specificity of 100% [Moderate quality evidence].
- No studies were retrieved on **culture** tests.

Diagnostic accuracy of tests for gonorrhoea using rectal samples

No studies were identified.

Diagnostic accuracy of tests for gonorrhoea using pharynx samples

No studies were identified.

Summary of results of diagnostic accuracy of tests for gonorrhoea in women

In Table 28, an overview is presented on the retrieved diagnostic accuracy of NAATs and culture tests in women.

Table 28 – Overview of the diagnostic accuracy to detect gonorrhoea in women

WOMEN	Vulvovaginal (self-taken)	Endocervical	Self-collected vaginal	Self-collected vaginal-posted	Clinician-collected vaginal	Urine
SDA	/	Sens: 87.5-98% Spec: 98.9-100% PPV: 88.0 -100.0%	Sens: 100% Spec: 99%	Sens: 80% Spec: 100%		Sens: 76.7-98% Spec: 95.6-100% PPV: 95.1-95.5%
TMA	Sens: 99% Spec: 100%	Sens: 90.6-100% Spec: 99-100% PPV: 87.0-100.0%	*TMA Combo:* Sens: 98.7 Spec: 99.6 *TMA NG:* Sens: 96.1 Spec: 96.3	Sens: 100% Spec: 100% PPV: 100.0%	Sens: 93.8-96.2% Spec: 99.3-99.7%	Sens: 82.6-97% Spec: 99.4-100% PPV: 95.4-100.0%
PCR	/	Sens: 87.1-100% Spec: 99.7-100% PPV: 97.0-98.0%	Sens: 95.7-100% Spec: 99.7-100%	Sens: 100% Spec: 99%	Sens: 95-97% Spec: 99-100% PPV: 45.5-93.3%	Sens: 87-100% Spec: 99.6-100% PPV: 90.0-100.0%
Culture	/	Sens: 81-86% Spec: 100%	/	/	/	/

In the GRADE profiles presented below (Table 29), an overview is presented of the number of studies per comparison, the quality assessment and the summary of findings (see also appendix 8.1 for the forest plots). These considerations served as a basis for the formulation of the conclusions and the recommendations.

Table 29 – GRADE profiles: Diagnostic tests for gonorrhoea in women, by sample type and assay

Study characteristics			Quality Assessment					Summary of findings Range % (95% CI)		
No. of studies	**Design**	**No.**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sensitivity (%)**	**Specificity (%)**	**Quality**
NAAT tests										
Women – vulvovaginal samples (self-taken) – TMA (prevalence: 2.5%)										
1	Diagnostic cohort study	3859	No serious risk of bias	Not applicable	No serious indirectness	No serious imprecision	None	99 (94-100)	100 (100-100)	HIGH
Women – endocervical samples – SDA (prevalence: 1.6%, 3.8%, 6.5% and 11.7%)										
4	Diagnostic cohort studies	8440	Serious risk of bias[2]	Serious inconsistency[3]	No serious indirectness	No serious imprecision	None	87.5 (71.0-96.5) to 98 (92-100)	98.9 (97.8-99.6) to 100 (100-100)	LOW
Women – endocervical samples – TMA (prevalence: 1.6%, 2.5%, 3.8%, 6.5% and 8.7%)										
5	Diagnostic cohort studies	13446	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	90.6 (75.0-98.0) to 100 (95-100)	99 (98-99) to 100 (100-100	HIGH
Women – endocervical samples – PCR (prevalence: 1.3%, 1.6%, 2.4% and 3.8%)										
4	Diagnostic cohort studies	11605	No serious risk of bias	Serious inconsistency[3]	No serious indirectness	No serious imprecision	None	87.1 (70.2-96.4) to 100 (85-100)	99.7 (99.0-100) to 100 (100-100)	MODERATE
Women – endocervical samples – LCR (prevalence: 8.7%)										
1	Diagnostic cohort studies	1489	Serious risk of bias[2]	Not applicable	No serious indirectness	No serious imprecision	None	96 (91-99)	100 (99-100)	MODERATE
Women – clinician-collected vaginal samples – TMA (prevalence: 3.8% and 5.4%)										
2	Diagnostic cohort studies	3478	Serious risk of bias[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	93.8 (79.2-99.2) to 96.2 (CI not reported)	Symptomatic: 99.3 (98.4-99.8) to 99.7 (98.99-100.0)	MODERATE
Women – clinician-collected vaginal samples – PCR (prevalence: 2.4% and 3.8%)										
2	Diagnostic cohort studies	4180	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	95 (85 to 99) to 97 (83-100)	99 (99-100) to100 (100-100)	HIGH

Women – self-collected vaginal samples – SDA (prevalence: 6.5% and 11.7%)										
2	Diagnostic cohort studies	2110	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	100 (92 to 100) to 100 (94-100)	99 (98-100) to 99 (99-100)	LOW
Women – self-collected vaginal samples – PCR (prevalence: 1.3% and 3.8%)										
2	Diagnostic cohort studies	5123	Serious risk of bias[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	95.7 (78.1-99.9) to 100 (85-100)	99.7 (98.9-100.0) to 100 (100-100)	MODERATE
Women – self-collected vaginal samples – TMA (prevalence: 3.8%)										
1	Diagnostic cohort studies	1464	Very serious risk of bias[1]	Not applicable	No serious indirectness	No serious imprecision	None	TMA Combo: 98.7 TMA NG: 96.1 (CI not reported)	TMA Combo: 99.6 TMA NG: 96.3 (CI not reported)	LOW
Women – vaginal self-collected – postal – SDA (prevalence: 1%)										
1	Diagnostic cohort study	500	Very serious risk of bias[1]	Not applicable	No serious indirectness	Very serious imprecision[4]	None	80 (28-99)	100 (99-100)	VERY LOW
Women – vaginal self-collected – postal - PCR (prevalence: 1%)										
1	Diagnostic cohort study	500	Very serious risk of bias[1]	Not applicable	No serious indirectness	Very serious imprecision[4]	None	100 (48-100)	99 (97-100)	VERY LOW
Women – vaginal self-collected – postal - TMA (prevalence: 1%)										
1	Diagnostic cohort study	500	Very serious risk of bias[1]	Not applicable	No serious indirectness	Very serious imprecision[4]	None	100 (48-100)	100 (99-100)	VERY LOW

Women – first catch urine samples – SDA (prevalence: 1.6, 3.8%, 6.5% and 11.7%)										
4	Diagnostic cohort studies	8440	Serious risk of bias[2]	Serious inconsistency[3]	No serious indirectness	Serious imprecision[4]	None	76.7 (57.7-90.1) to 98 (92-100)	95.6 (93.7-97.0) to 100 (100-100)	VERY LOW
Women – first catch urine samples – PCR (prevalence: 0.3%, 1.3%, 1.6%, 2.5% and 3.8%)										
5	Diagnostic cohort studies	11540	No serious risk of bias	Serious inconsistency[3]	No serious indirectness	No serious imprecision	None	87.0 (66.4-97.2) to 100 (16-100)	99.6 (98.7-99.9) to 100 (100-100)	MODERATE
Women – first catch urine samples – TMA (prevalence 1.6%, 2.5% and 3.8%)										
3	Diagnostic cohort studies	8098	No serious risk of bias	Serious inconsistency[3]	No serious indirectness	No serious imprecision	None	82.6 (61.2-95.0) to 97 (89-100)	99.4 (98.5-99.8) to 100 (100-100)	MODERATE
Culture test										
Women – endocervical samples (prevalence: 2.5% and 8.7%)										
2	Diagnostic cohort studies	5348	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	81 (72-88) to 86 (79-91)	100 (100-100) to 100 (100-100)	HIGH

[1] Risk of bias was assessed using the QUADAS-2 checklist. If there was one criterion with a high risk of bias the study was considered to have a serious risk of bias. If there were two or more criteria with a high risk of bias the study was considered to have a very serious risk of bias. The evidence was downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

[2] Risk of bias was assessed using the QUADAS-2 checklist. If there was one criterion with a high risk of bias the study was considered to have a serious risk of bias. If there were two or more criteria with a high risk of bias the study was considered to have a very serious risk of bias. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias.

[3] Inconsistency was assessed by inspection of the sensitivity (considered to be the primary measure for this review) using the point estimate of individual studies on the forest plots. The evidence was downgraded by 1 increment if the individual study comparisons varied across 2 areas [(for example, 50–90% and 90–100%)] and by 2 increments if the individual study comparisons varied across 3 areas [(for example, 0–50%, 50–90% and 90–100%)].

[4] Imprecision was based on the range of point estimates or, if only one study contributed to the evidence, the 95% CI around the single study. As a general rule a variation of 0–20% was considered precise, 20–40% serious imprecision, and >40% very serious imprecision. Imprecision was assessed on the primary outcome measure for decision-making.

Diagnostic accuracy of gonorrhoea combined Aptima Combo tests with chlamydia in women

Three studies[36, 37, 46] reported the diagnostic accuracy of the TMA Aptima Combo to detect chlamydia in women, using endocervical samples,[37, 46] self-collected vaginal samples[36] or urine samples.[46]

In the GRADE profiles tabulated below (Table 30), an overview is presented of the number of studies per comparison, the quality assessment and the summary of findings. These considerations served as a basis for the formulation of the conclusions and the recommendations.

Table 30 – GRADE profiles: Diagnostic tests for chlamydia in women, by sample type

Study characteristics			Quality Assessment					Summary of findings Range %(95% CI)		
No. of studies	**Design**	**No.**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sensitivity (%)**	**Specificity (%)**	**Quality**
Women – endocervical samples – TMA										
2	Diagnostic cohort studies	5722	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	97 (94-98) to 99 (97-100) Symptomatic: 91.4 (83.0-96.5) Asymptomatic: 78.7 (64.3-89.3)	97 (96-98) to 99 (99-99) Symptomatic: 99.4 (98.5-99.8) Asymptomatic: 98.6 (97.4-99.4)	HIGH
Women – first catch urine samples – TMA										
1	Diagnostic cohort studies	4311	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	96 (93 to 98) Symptomatic: 93.8 (86.2-98.0) Asymptomatic: 93.5 (82.1-98.6)	100 (99 to 100) Symptomatic: 99.4 (98.5-99.8) Asymptomatic: 99.2 (98.2-99.8)	MODERATE
Women – self-collected vaginal sample posted to laboratory – TMA										
1	Diagnostic cohort studies	1000	Very serious risk of bias	Not applicable	No serious indirectness	No serious imprecision	None	100.0% (96.1-100)	100.0% (99.6-100)	LOW

3.2.2.6 *Clinical outcomes of tests for gonorrhoea in women*

User friendly aspects of the tests

One study[34] reported the outcomes of a survey on preferred collection method for the samples for women in their study. 2009 women out of the study total of 2014 responded. The most preferred method of sample collection was self-collected vaginal swabs (30.5%) followed by urine specimen in 26% and least preferred was clinician-collected vaginal swab 14%. 30% of the respondents had no preference.

Harmful effects

The outcomes on harms, such as pain or discomfort, were not reported.

3.2.2.7 *Conclusions: Diagnostic accuracy of tests for gonorrhoea in women*

Vaginal, endocervical and urine

- **The NAAT tests showed a higher sensitivity compared to culture, when used with endocervical sample from women to diagnose gonorrhoea.**
- **Differences between diagnostic accuracy of TMA, PCR and SDA were NOT present, therefore it can be stated that the type of NAAT test will not influence the diagnostic testing.**
- **The sensitivities of NAAT tests (TMA, PCR and SDA) for cervical and vaginal samples were equivalent, but slightly lower but still acceptable for first-void urine samples.**
- **The TMA Combo test obtained high sensitivity when used with endocervical or first-void urine samples from women to diagnose both C. trachomatis and N. gonorrhoea.**
- **A higher sensitivity was found in self-collected vaginal samples compared to clinician-collected samples.**
- **The 'at home self-collected' vaginal specimens posted to the lab showed sensitivities of 100% for the PCR and TMA but a sensitivity of 80% for the SDA.**

Rectal

- **Evidence for rectal samples is limited and is available only from one study combining results for men and women.**
- **The NAAT tests showed a higher sensitivity compared to culture, when used with rectal sample from women to diagnose gonorrhoea.**
- **PCR was not evaluated in rectal samples.**
- **TMA had a higher sensitivity compared to SDA.**

Oropharyngeal

- **No evidence was available.**

3.2.2.8 *Conclusions: Clinical outcomes of tests for gonorrhoea in women*

- **From the patients' perspective, the preferred method of sample selection was self-collected vaginal swabs compared to clinician-collected vaginal swabs.**
- **No conclusions can be drawn on harms as there was no evidence for this outcome.**

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Clinical evidence: • The evidence shows a higher diagnostic accuracy of NAAT tests compared to culture tests. • Based on the sensitivity results, vaginal samples should be considered as first option, secondly urine sample. • No evidence was retrieved on pharyngeal swabs. The IUSTI guideline[2] recommends to use an oropharyngeal swab in women who engage in receptive oral sex. • Limited evidence was retrieved on rectal swabs. The TMA performed better than the SDA. Further, the IUSTI guideline[2] recommends to use a rectal swab in women who engage in receptive anal sex, even if these tests are not EC-approved. • No evidence was reported on potential harms. • Risk for false positives and false negatives in tests with lower sensitivity and specificity.
Quality of evidence	Update literature search: 12 diagnostic studies ranging from very low quality to high quality evidence. Differences in sensitivity can be explained by the testing procedure (swab collection, time to transportation and storage conditions) in clinical practice compared to research settings.
Costs (resource allocation)	Testing from multiple sites in individuals with high risk sexual behaviour is expensive. Therefore, pooling of samples, thereby reducing the number of samples from 3 to 2 or even 1 may benefit the patient especially if testing is to be repeated every 3 to 6 months. The pooling of an oropharyngeal, urine/urethral and rectal sample on site (clinician) or in the laboratory are both an area of research. Laboratory pooling has recently been tried in Belgium in MSM and although NAAT inhibition improved, the study was too small to draw firm conclusions. [99] Requirements and costs are related to the sampling process, laboratory set up, analysis process, workforce and hours. Postal self-collected: is not performed in clinical practice.
Patients values and preferences	Preference of women for self-collected vaginal swabs. Diagnostic procedures for minors: If the professional considers that the child is mature enough to give his or her consent, his/her informed consent is sufficient (art. 12 § 2 of the Patient Rights Act). The professional is not only guided by the age and maturity of the child, but also by the nature and consequences of the intervention or treatment.[100] As the severity of the procedure and the associated risks increase, the maturity requirements will also be higher. Competent minors can independently decide on low-risk medical interventions. These may include tests or treatments with few side effects (e.g., taking blood samples, prescribing contraceptives, etc.) or interventions that pose few health risks (e.g. tooth extraction, etc.). Conducting an STI diagnostic test is a low-risk procedure. It is important to note that this concerns the ability to accept a diagnostic test. This should be distinguished from the ability to authorise acts that affect sexual integrity. Just because you were not legally considered capable of consenting to sexual intercourse does not mean that you could not legally consent to a (medical) act that is indirectly related to sexual intercourse (theoretically punishable).
Aspects related to clinical practice	Urine sample: what is the ideal time interval for ‘time since last urinating’ to consider in providing a sample? GDG: 1 hour interval

3.2.3 Recommendations: Who to test for gonorrhoea

Who to test for gonorrhoea	Strength of Recommendations	Level of Evidence
A. Patients with symptoms suspicious of gonorrhoea.	Weak	Very low
B. For asymptomatic patients with high risk sexual behaviour or at increased risk for gonorrhoea: 1. Sex worker of any gender 2. MSM with high risk behaviour • unprotected sexual contacts in non-exclusively monogamous relationships • who are on Pre-exposure prophylaxis (PrEP) • with a recent chlamydia, HIV or syphilis diagnosis 3. a) Patient or sex partner originates or travels to and from countries that are most affected: The WHO regions most affected are the African region, the Western Pacific region and the Americas. b) Patient or sex partner originates or travels to and from countries where multi-drug resistant gonorrhoea is prevalent: Southeast and East Asian countries 4. Heterosexual patient with unprotected oral, anal or vaginal intercourse in non-exclusively monogamous relationships with/whenever • concurrent partners • multiple partners over a short time period • partner as defined above in classification 1, 2, or 3 • an STI diagnosis in the past year • partners in anonymous setting 5. Adolescents and young people up to the age of 29 years • who prefer to stop using condoms with their partner (expressed during a sexual health consultation) • who have unprotected oral, anal or vaginal intercourse in non-exclusively monogamous relationships with/whenever o concurrent partners o multiple partners over a short time period o partner as defined above in classification 1, 2, or 3	Weak	Very low

C. All pregnant women in the first trimester or at the first antenatal visit if she or her partner belongs to classification 1 to 5. For pregnant women with high risk sexual behaviour or at increased risk for gonorrhoea as identified above, repeat test in the third trimester.	Weak	Very low
D. Test for gonorrhoea whenever: • a baby that is born while the mother has an active infection • in case of abortion • sexual partner with suspected or confirmed gonorrhoea • all patients who are newly diagnosed with an STI including HIV • patients with a newly diagnosed hepatitis B or hepatitis C that may have been acquired through sexual transmission	Weak	Very low

3.2.4 *Recommendations: Diagnostic tests for gonorrhoea in men*

Diagnostic tests for gonorrhoea in men	Strength of Recommendations	Level of Evidence
For asymptomatic and symptomatic men, offer NAAT test(s) from one or more sample sites according to their sexual behaviour o Insertive position (vaginal, anal, or oropharyngeal): use a first flow urine (asymptomatic) or an urethral sample (symptomatic) for a combined gonorrhoea-chlamydia NAAT o Anal receptive position: use a anorectal sample for a combined gonorrhoea-chlamydia NAAT o Oropharyngeal receptive position: use an oropharyngeal sample for a gonorrhoea NAAT	Strong	Urine and urethral: low (SDA), moderate (TMA) and high (PCR). Rectal and pharyngeal: very low (SDA, TMA)
For men who have sex with men known to have high sexual risk behaviour: sample all three sites	Weak	Very low
The use of a NAAT test on pooled samples (oropharyngeal, urine/urethral and rectal) was evaluated in one study. Currently, we suggest that 1st line healthcare practitioners take separate samples and send them to the laboratories with a prescription detailing the level of risk. There, a decision can be taken to use a NAAT test on pooled samples in specific situations (e.g. high risk setting, need for repetitive testing) when in-house validated technology and expertise is available.	Weak	Moderate
In men, do NOT offer culture testing for initial diagnosis.[µ]	Strong	Rectal: low to moderate. Pharyngeal: very low.

[µ]Symptomatic men suspected of gonorrhoea could contribute to antimicrobial resistance surveillance and a culture should be taken at initial diagnosis, especially if they are treated presumptively (see recommendation 0).

3.2.5 Recommendations: Diagnostic tests for gonorrhoea in women

Diagnostic tests for gonorrhoea in women	Strength of Recommendations	Level of Evidence
For asymptomatic and symptomatic women, offer NAAT test(s) from one or more sample sites according to their sexual behaviour:		
• Vaginal receptive intercourse: use either (self-collected or clinician-collected) vaginal or first flow urine samples for a combined gonorrhoea-chlamydia NAAT	Strong	Vaginal samples: low to moderate (self-collected); moderate to high (clinician-collected). Endocervical samples: low to high. Urine sample: very low (SDA) to moderate (TMA and PCR).
• Oral receptive: oropharyngeal sample for a gonorrhoea NAAT	Weak	Very low
• Receptive anal: anorectal sample for a combined gonorrhoea-chlamydia NAAT	Weak	Rectal: moderate (SDA) to high (TMA)
For women with high sexual risk behaviour: offer NAAT test(s) from all three sites.	Weak	Very low
In women, do NOT offer culture testing for initial diagnosis.	Strong	High
Research recommendation: To perform a study in women with sexual high risk behaviour with pooling of urine or vaginal, pharyngeal and anorectal samples.		

3.2.6 Diagnosis of gonorrhoea: Good practice statements

Diagnosis of gonorrhoea: Good practice statements
The ideal time interval for time since last urinating to consider in providing a sample is 1 hour.
First flow (first-void) urine sample is preferred over midstream sample both for chlamydia and gonorrhoea.
Specimen collection swabs for *C. trachomatis* / *N. gonorrhoea* NAAT and gonorrhoea culture must be synthetic. Other materials (e.g. cotton wool, wood) might inhibit testing (CDC, 2014).[101]
Urethral specimen collection for *C. trachomatis/ N. gonorrhoea* is invasive requiring insertion of a swab 2–3 cm into the male urethral followed by two or three rotations to collect sufficient cells.[101] Urine specimens are less invasive and are preferred over urethral specimens.
For the clinician, to collect an oropharyngeal swab, use a wooden tongue depressor to hold the tongue in place; without touching the sides of the mouth, use a sterile swab to swab the posterior nasopharynx and the tonsillar arches.[101]

3.3 Treatment of gonorrhoea: Information and advice for the patient

3.3.1 Recommendations from international guidelines

Table 31 – Recommendations from international guidelines – Information for the patient

Source	Recommendation for 1st line
INFORMATION, EXPLANATION AND ADVICE FOR THE PATIENT	
IUSTI 2012[2]	Patients should be advised to abstain from sexual contact for seven days after they and their partners have completed treatment and their symptoms have resolved (IV; C); Patients (and their sex partners) should be given information about their infection, including details about transmission, prevention and complications. It is recommended that both verbal and written information be provided (IV; C); A patient information leaflet is available on the IUSTI–Europe website for guidelines (http://www.iusti.org/regions/Europe/euroguidelines.htm).
CDC 2015[12]	To minimize disease transmission, persons treated for gonorrhoea should be instructed to abstain from sexual activity for 7 days after treatment and until all sex partners are adequately treated (7 days after receiving treatment and resolution of symptoms, if present). All persons who receive a diagnosis of gonorrhoea should be tested for other STIs, including chlamydia, syphilis, and HIV.

3.3.2 Recommendations regarding information and advice for the patient

Gonorrhoea information and advice for the patient	Strength of Recommendations	Level of Evidence
Patients should be advised to abstain from sexual contact for seven days after they and their partners have completed treatment and their symptoms have resolved.	Weak	Very low
All persons who receive a diagnosis of gonorrhoea should be tested for other STIs, including chlamydia, syphilis, and HIV.	Weak	Very low
Patients (and their sex partners) should be given information about their infection, including details about transmission, prevention and complications. Verbal information needs to be reinforced with written support or video material such as, hyperlinks towards scientific websites or organisations dedicated to STIs leaflets, brochures.	Weak	Very low

The following Belgian websites contain useful information for patients:

- https://depistage.be/ (French)
- https://www.sidasos.be/ (French)
- https://www.sensoa.be/ (Dutch)
- http://www.alias-bru.be/ (for male sex workers; Dutch, French, English)
- https://domusmedica.be/richtlijnen/steekkaarten-implementatiemateriaal?s=hiv (Dutch) for HIV testing guidance Flanders – Hermetic: HIV European Research on Mathematical Modelling & Experimentation of HIV Testing In hidden Communities; https://www.medischcentrumhuisartsen.be/documents/focus/agenda/downloads.xml?loc=&lang=nl (Dutch)
- https://domusmedica.be/richtlijnen/themadossiers/themadossier-seksueel-overdraagbare-infecties (Dutch)
- Digital anonymous platform to inform sexual partners in case of a STD diagnosis: https://www.partneralert.be (Dutch and French)
- Vaccination for hepatitis B for adults: Hoge gezondheidsraad: https://www.health.belgium.be/nl/advies-8816-vaccinatie-volwassenen-hepatitis-b; https://www.health.belgium.be/en/node/20219
- Vaccination hepatitis B adolescents: https://www.health.belgium.be/nl/advies-8809-vaccinatie-tegen-hepatitis-b-kinderen-en-adolescenten
- http://www.hivsam.be/fr/: The HIV-SAM Project supports HIV prevention and sexual health promotion with Sub-Saharan African Migrants (SAM) in Flanders.

3.4 Treatment of gonorrhoea: timing of initiation of therapy

3.4.1 Recommendations from international guidelines

Table 32 – Recommendations from international guidelines - Timing of initiation of therapy

Source	Recommendation for 1st line
INITIATION OF THERAPY	
IUSTI 2012[2]	Indications for therapy (IV; C) • Identification of intracellular diplococci at a genital site by Gram stain or Methylene blue-stain microscopy; • Positive culture or confirmed NAAT from any site for *N. gonorrhoeae* (or unconfirmed NAAT from urogenital specimens in settings where PPV>90%); • On epidemiological grounds, if a recent partner has confirmed gonococcal infection; • On epidemiological grounds, mother of neonate with confirmed gonococcal infection; • On epidemiological grounds, treatment can be considered following sexual assault; • On demonstration of a purulent urethral discharge in men or mucopurulent cervicitis in women when rapid diagnostic tests are not available and after specimen collection for laboratory testing. In this circumstance, combined treatment for gonococcal and chlamydial infection should always be given.
CDC 2015[12]	Presumptive treatment: • cervicitis in women at increased risk (e.g., those aged <25 years and those with a new sex partner, a sex partner with concurrent partners, or a sex partner who has a STI). Treatment to include chlamydia treatment; • if follow-up cannot be ensured; • urethritis (discharge on examination OR Gram stain demonstrating white blood cells OR positive urine leucocyte esterase test). Treatment to include chlamydia; • mothers of babies with gonorrhoea.

3.4.2 Recommendations regarding testing and surveillance for resistance

Gonorrhoea testing and surveillance for resistance	Strength of Recommendations	Level of Evidence
In case of suspected or confirmed gonorrhoea after travelling to Southeast and East Asia (suspicion for resistant gonorrhoea[μ]) the following measures should be taken (if not already done): • Take a detailed travel history to elicit assumed location (country, region) of infection • Sample all potentially infected sites for culture and NAAT	Weak	Very low
In case of highly suspicious symptomatic gonorrhoea take both a NAAT and culture before treatment is started.	Weak	Very low
Before treatment is given • At the time of the consultation for a positive gonorrhoea NAAT test, a sample should be taken for culture (if not already done). This pre-treatment culture sample is needed for the surveillance activities for gonorrhoea resistance in Belgium.	Weak	Very low

Note. [μ] The Belgian resistance data are presented in section 3.6.2 and Table 35.

3.4.3 Recommendation regarding initiation of therapy

Initiation of therapy for gonorrhoea	Strength of Recommendation	Level of Evidence

Treatment is to be started for the following reasons:
• Positive culture or NAAT from any site for *N. gonorrhoea*
• Without waiting for the results of the diagnostic tests:
  o On epidemiological grounds
  ▪ if a recent partner has confirmed gonococcal infection
  ▪ mother of neonate with confirmed gonococcal infection
  o In case of symptoms and after specimen collection for laboratory testing
  ▪ purulent urethral discharge in men
  ▪ proctitis in men who have sex with men
  ▪ mucopurulent cervicitis in women
  o If follow-up cannot be assured and after specimen collection for laboratory testing
	Weak	Very low

3.5 Treatment of gonorrhoea: When to refer to second line

3.5.1 Recommendations from international guidelines

Cases of complicated gonorrhoea are to be referred for second line care. This means to the appropriate specialist or medical colleague knowledgeable in gonorrhoea who consults at a dedicated STI / HIV clinic or an infectious disease clinic or hospital. No precise definition of what constitutes a complicated gonorrhoea case was found in the guidelines searched. Nevertheless, guidelines do offer guidance on when to consider gonorrhoea as uncomplicated and complicated. This is summarised for complicated gonorrhoea in Table 33.

Table 33 – International guidelines – description complicated gonorrhoea

Source	
COMPLICATED GONORRHOEA AND SPECIFIC SITUATIONS	
IUSTI 2012[2]	Complicated gonorrhoea: - Upper genital tract infection: epididymo-orchitis and pelvic inflammatory disease - Disseminated gonococcal infection Gonococcal conjunctivitis in adults
CDC 2015[12]	Complications of gonorrhoea: - Disseminated gonococcal infection - Arthritis and arthritis-dermatitis syndrome - Pelvic inflammatory disease Cervicitis with a suspicion of pelvic inflammatory disease Urethritis with a suspicion of other organisms than *N. gonorrhoea*

3.5.2 Referral to the second line for gonorrhoea: Good practice statements

When to refer to the second line[μ] for gonorrhoea: Good practice statements
Patients should be referred to the second line **before initiation of treatment**: • When first line therapy is not available or cannot be tolerated (failed) by patient • When cephalosporin allergy is already known or documented • When the patient presents with complicated[£] gonorrhoea
Patients should be referred to the second line **at the time of treatment failure:** • When first line treatment fails based on symptoms or laboratory testing • When the antibiotic sensitivity report indicates resistance to ceftriaxone and/or azithromycin

Note. [μ] Referral to the appropriate specialist or medical colleague knowledgeable in gonorrhoea who consults at a dedicated STI / HIV clinic or an infectious disease clinic or hospital, is guided by the symptoms and their severity, or other characteristics such as pregnancy. [£]Complicated gonorrhoea defined as upper genital tract infection i.e. epididymo-orchitis and (suspicion of) pelvic inflammatory disease, disseminated gonococcal infection, gonococcal conjunctivitis in adults, arthritis and arthritis-dermatitis syndrome.

3.6 Treatment of gonorrhoea: Refining according to antimicrobial resistance

3.6.1 Recommendations from international guidelines

Table 34 – Recommendations from international guidelines - Refining treatment according to antimicrobial resistance

Source and target population	Recommendation for 1st line
UNCOMPLICATED GENITAL AND ANORECTAL GONOCOCCAL INFECTIONS	
WHO 2016[22] Target population: adults, adolescents (10–19 years of age), people living with HIV, and key populations, including sex workers, MSM and transgender persons	Local resistance data should determine the choice of therapy (both for dual therapy and single therapy) (Good practice statement).
WHO 2016[22] Target population: adults, adolescents (10–19 years of age), people living with HIV, and key populations, including sex workers, MSM and transgender persons	In settings where local resistance data are not available, the WHO STI guideline suggests dual therapy over single therapy for people with genital or anorectal gonorrhoea (Conditional recommendation, low quality evidence).

WHO recommends that treatment guidelines are refined based on data from recent and quality-assured gonococcal antimicrobial resistance (AMR) surveillance and that the use of an antimicrobial in empiric treatment is discontinued when the rates of therapeutic failures and/or antimicrobial resistance reach a level of 5%.[22]

3.6.2 Antimicrobial resistance: Belgian data

For the year 2016, 597 isolates of *N. gonorrhoea* were tested for the minimum inhibitory concentration (MIC) at the National Reference Centre for gonorrhoea, Institute of Tropical Medicine, Antwerp, Belgium.[5] The isolates originated from a total of 75 Belgian laboratories and 76.9% were originally from men, 20.7% from women and for 2.4% gender was not specified. The MIC (mg/L) was defined for azithromycine, ceftriaxone, ciprofloxacine, spectinomycine, cefixime, and penicillin based on the agar dilution method following the guideline of the Clinical and Laboratory Standards Institute (CLSI), and the European Committee on Antibiotic Susceptibility Testing (EUCAST). The Belgian reference laboratory is applying the EUCAST method as the standard from samples from 2017 onwards. The 2018 surveillance of STIs report presents both the CLSI and the EUCAST resistance data for gonorrhoea.

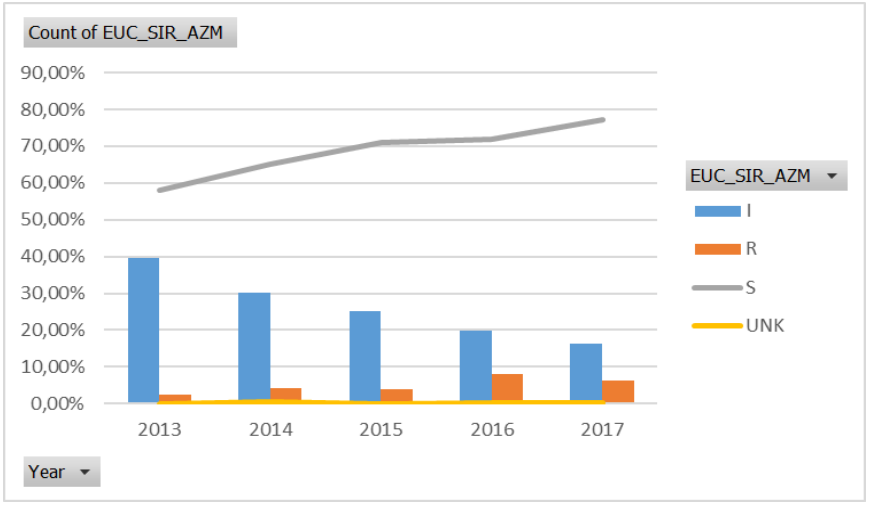
All isolates were sensitive for ceftriaxone and spectinomycine (CLSI and EUCAST). Resistance for azithromycine was present in 8.0% of isolates (CLSI and EUCAST) (Table 35). The resistance for azithromycin was higher compared to 2015 when 4.1% of isolates were resistant. Resistance has been documented previous to this date, with a variation over the years: 2% (2006), 8% (2010) and 1% (2012). The recent results are presented in Appendix 10 and originate from a Sciensano report.[5] Data from 2017 for ceftriaxone and azithromycin show a stable trend for azithromycin and an increase for the ceftriaxone resistance to 0.34% from 2015 to 2017 (Figure 4, personal communication T Crucitti, National Reference Centre).

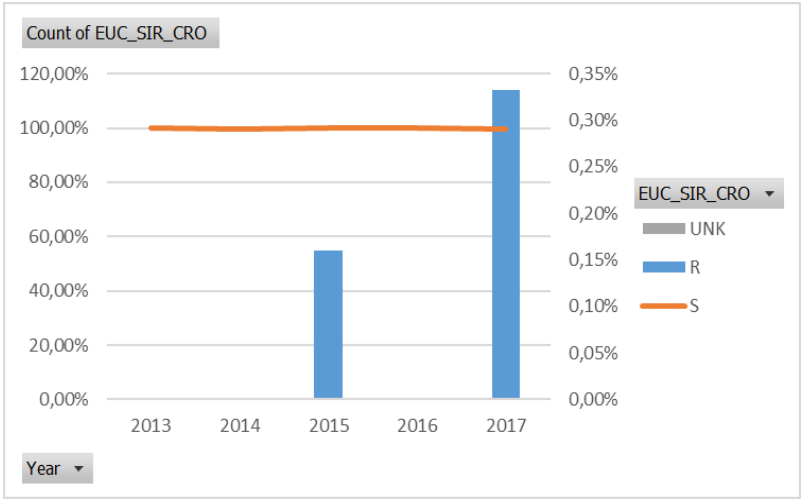
Table 35 – Minimum inhibitory concentrations for gonorrhoea 597 isolates 2016 Belgium by the EUCAST

Sensitivity isolates	Sensitive		MIC*	Intermediate sensitive		MIC*	Resistant		MIC*
Antibiotic	**N**	**%**	**mg/L**	**N**	**%**	**mg/L**	**N**	**%**	**mg/L**
Ceftriaxone	597	100.0	≤ 0.125	-	-	-	0	0.0	>0.125
Cefixime	561	94.0	≤ 0.125	-	-	-	36	6.0	>0.125
Azithromycine	428	71.7	≤ 0.25	121	20.3	0.5	48	8.0	>0.5
Spectinomycine	597	100.0	≤ 64	-	-	-	0	0.0	>64
Penicilline	69	11.6	≤ 0.06	369	61.8	0.125 - 1.0	159	26.6	≥ 2.0
Ciprofloxacine	321	53.8	≤ 0.03	2	0.3	0.06	274	45.9	>0.06
Tetracycline	256	42.9	≤ 0.5	142	23.8	1.0	199	33.3	>1

Source: Vanden Berghe et al. 2018.[5]
*Note. *MIC: Minimum inhibitory concentration*

Figure 4 – Evolution of antimicrobial resistance for gonorrhoea in Belgium – 2013 - 2017





Source: Data and slides are provided by the National Reference Centre for gonorrhoea Belgium.
Note. I: intermediate resistance; R: resistant; S: sensitive; Unk: unknown. £ resistance % on the right side of the figure; sensitivity % on the left side of the figure

3.7 Treatment of gonorrhoea: Treatment choice in men and women

3.7.1 Recommendations from international guidelines

Source and target population	Recommendation for 1st line	Remarks	Alternatives
UNCOMPLICATED GENITAL AND ANORECTAL GONOCOCCAL INFECTIONS			
WHO 2016[22] Target population: adults, adolescents (10–19 years of age), people living with HIV, and key populations, including sex workers, MSM and transgender persons **including pregnant women.**	***Dual therapy (one of the following)*** • ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose • cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose ***Single therapy (one of the following, based on recent local resistance data confirming susceptibility to the antimicrobial)*** • ceftriaxone 250 mg IM as a single dose • cefixime 400 mg orally as a single dose • spectinomycin 2 g IM as a single dose. (Conditional recommendation, low quality evidence).	Alternative single-medicine therapies, such as gentamicin or kanamycin, have not been suggested due to lack of surveillance data. Overall, the GDG agreed that the success of the available treatments is based on in vitro susceptibility of gonococcal infections, and should therefore be based on recent local surveillance data. The GDG agreed that dual therapy should be suggested due to the emergence of resistance and the paucity of surveillance data in most settings to guide decisions about susceptibility to single therapy.	
CDC 2015[12]	***Dual therapy*** Ceftriaxone 250 mg IM in a single dose PLUS Azithromycin 1g orally in a single dose	As dual therapy, ceftriaxone and azithromycin should be administered together on the same day, preferably simultaneously and under direct observation.	Use of ceftriaxone or cefixime is contraindicated in persons with a history of an IgE-mediated penicillin allergy (e.g., anaphylaxis, Stevens Johnson syndrome, and toxic epidermal necrolysis). Potential therapeutic options re dual treatment with single doses of oral gemifloxacin 320 mg plus oral azithromycin 2 g or dual treatment with single doses of intramuscular

			gentamicin 240 mg plus oral azithromycin 2 g. Spectinomycin for treatment of urogenital and anorectal gonorrhoea can be considered when available.
	If ceftriaxone is not available: Cefixime 400 mg orally in a single dose PLUS Azithromycin 1 g orally in a single dose		
IUSTI 2012[2] **Adults and adolescents**	***Dual therapy*** Ceftriaxone 500 mg intramuscularly as a single dose together with azithromycin 2 g as single oral dose (IV; C). If ceftriaxone 500 mg for intramuscular injection is not available, the intramuscular suspension can be mixed as follows: 3.5 mL of 10 mg/mL (1%) lidocaine without adrenalin is suspended into a 1 g vial of ceftriaxone and mixed. Two millilitres of the mixture is drawn and injected intramuscularly	Azithromycin tablets may be taken with or without food but gastrointestinal side-effects can be less if taken after food. Co-infection with C. trachomatis is common in young (<30 years) heterosexual patients and MSM with gonorrhoea. If treatment for gonorrhoea does not include azithromycin, treatment with azithromycin 1 g oral as a single dose or doxycycline 100 mg oral dose twice daily for seven days should be given for possible chlamydial co-infection unless co-infection has been excluded with NAAT testing.	Cefixime 400 mg oral as a single dose (Ib; A) together with azithromycin 2 g as a single oral dose (IV; C); Ceftriaxone 500 mg intramuscularly as a single dose (IV; C); Spectinomycin 2 g intramuscularly as a single dose (Ib; A) together with azithromycin 2 g as a single oral dose (IV; C).
IUSTI 2012[2] **Adults and adolescents**	Fluoroquinolones cannot generally be recommended for the treatment of gonorrhoea because of the worldwide high prevalence of quinolone resistance. When an infection is known before treatment to be fluoroquinolone sensitive, based on appropriate laboratory susceptibility testing and there are indications against using ceftriaxone, ciprofloxacin 500 mg oral as a single dose or ofloxacin 400 mg oral as a single dose have proven high efficacy (Ib; A).		Recommended treatment for patients with a history of penicillin anaphylaxis or cephalosporin allergy: Spectinomycin 2 g intramuscularly as a single dose (Ib; A) together with azithromycin 2 g oral single dose. Alternative treatments in patients with known penicillin

			anaphylaxis or cephalosporin allergy when fluoroquinolone or azithromycin sensitivity has been confirmed by appropriate laboratory susceptibility testing: Ciprofloxacin 500 mg oral as a single dose or ofloxacin 400 mg oral as a single dose or azithromycin 2 g as a single oral dose (Ib; B).
IUSTI 2012[2] **Men with acute epididymo-orchitis**	Ceftriaxone 500 mg intramuscularly as a single dose together with doxycycline 100 mg oral dose twice daily for 10–14 days (IV; C).		Ciprofloxacin 500 mg as a single oral dose may be used as an alternative to ceftriaxone when sensitivity confirmed by appropriate laboratory susceptibility testing.
UNCOMPLICATED OROPHARYNGEAL GONOCOCCAL INFECTIONS			
WHO 2016[22] Target population: adults, adolescents (10–19 years of age), people living with HIV, and key populations, including sex workers, MSM and transgender persons including pregnant women.	Dual therapy is recommended over single therapy ***Dual therapy (one of the following)*** • ceftriaxone 250 mg IM as a single dose PLUS azithromycin 1 g orally as a single dose • cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose Single therapy (based on recent local resistance data confirming susceptibility to the antimicrobial) • ceftriaxone 250 mg IM as single dose. (Conditional recommendation, very low quality evidence).	Treatment failures have been observed after single therapy for gonococcal oropharyngeal infections and therefore dual therapy is suggested over single therapy.	
CDC 2015[12]	***Dual therapy*** Ceftriaxone 250 mg IM in a single dose PLUS Azithromycin 1g orally in a single dose	To minimize disease transmission, persons treated for gonorrhoea should be instructed to abstain from sexual activity for 7 days after treatment and until all sex partners are adequately treated (7 days after receiving treatment and resolution of symptoms, if present).	Use of ceftriaxone or cefixime is contraindicated in persons with a history of an IgE-mediated penicillin allergy (e.g., anaphylaxis, Stevens Johnson syndrome, and toxic epidermal necrolysis).

		Potential therapeutic options re dual treatment with single doses of oral gemifloxacin 320 mg plus oral azithromycin 2 g or dual treatment with single doses of intramuscular gentamicin 240 mg plus oral azithromycin 2 g. Spectinomycin for treatment of urogenital and anorectal gonorrhoea can be considered when available.
IUSTI 2012[2] **Adults and adolescents**	***Recommended treatment for pharyngeal infection*** Ceftriaxone 500 mg intramuscularly as a single dose together with azithromycin 2 g oral single dose (IV; C)	Ceftriaxone 500 mg intramuscularly as a single dose (IV; C). This regimen is only an alternative option if azithromycin is not available or patient is unable to take oral medication. Alternative treatments for pharyngeal infection when there is a history of penicillin anaphylaxis or cephalosporin allergy and fluoroquinolone or azithromycin resistance are excluded by appropriate laboratory susceptibility testing: Ciprofloxacin 500 mg as a single oral dose or ofloxacin 400 mg as a single oral dose or azithromycin 2 g as a single oral dose.

Source and target population	Recommendation for 1st line	Remarks	Alternatives
TREATMENT OF CHLAMYDIA AND UNCOMPLICATED GONORRHOEA CO-INFECTION			
BASHH 2015[102, 103] Target population: individuals aged 16 years and older	***Dual therapy*** • ceftriaxone 500 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose (IV, C) ***If gonorrhoea + rectal chlamydia*** • ceftriaxone 500 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose PLUS doxycycline 100mg bd for seven days (IV, C) ***If gonorrhoea + LGV*** • ceftriaxone 500 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose PLUS doxycycline 100mg bd for 21 days (IV, C)		

3.7.2 Recommendations from national guides

Table 36 – Recommendations from national guides – Molecules and dosages for adults and adolescents

Guide	Indication	Combination treatment first choice	Combination treatment second choice	Single treatment
BCFI 2018	Urethritis/gono	Ceftriaxone 500 mg Azithromycin 2 g	Ceftriaxone 500 mg Doxycycline 2x100 mg 7 days	
BAPCOC 2012 (first line)	Gono	Ceftriaxone 500 mg Azithromycin 2 g	Spectinomycin 2 g[a] Azithromycin 2 g	Ciprofloxacin 500 mg OR Ofloxacin 400 mg OR Levofloxacin 250 mg
	Urethritis	Ceftriaxone 500 mg Azithromycin 2 g		
BAPCOC 2017 (hospitals)	Gono without complications	Ceftriaxone 500 mg MIN; Azithromycin 2g	Spectinomycin 2g doxycycline 200mg 7/7 OR Spectino 2g azithromycin 2g	Ceftriaxone min 500mg (if azithro contra indicated)
BVIKM/SBIMC[b]	Gono without complications	Ceftriaxone 1g; Azithromycin 2g	Spectinomycin 2g doxycycline 200mg 7/7 OR Spectino 2g azithromycin 2g	
Agentschap zorg en gezondheid 2017	Gono without complications	Ceftriaxone minimum 500 mg Azithromycin 2 g		Quinolone** OR Azithromycin 2 g**
Domus Medica 2017	Gono without complications	Ceftriaxone 500 mg Azithromycin 2 g		
Ghapro 2014	Gono	Ceftriaxone 500 mg Azithromycin 2 g		

Note. [a] Spectinomycine is active against gonorrhoea. The sole indication is gonorrhoea infections when ceftriaxone cannot be used due to allergy or resistance. BCFI: Belgisch Centrum voor Farmacotherapeutische Informatie; CBIP: Centre belge d'information pharmacothérapeutique; BAPCOC: Belgian Antibiotic Policy Coordination Committee; [b]BVIKM: Belgische vereniging voor infectiologie en klinische microbiologie; SBIMC: Société belge d'infectiologie et de microbiologie clinique

3.7.3 Additional literature search: Treatment of gonorrhoea in women and men, including young people

The World Health Organisation (WHO) Guidelines for the treatment of *N. gonorrhoeae* (2016)[22] identified 46 studies that were ordered for this question. All the studies were excluded as the studies were quite old and considered to no longer be relevant in light of the current resistance data (see excluded studies list in the Appendix 2.3). Two RCTs[52, 56] were identified from the update search and included. Due to the lack of evidence for this question, two conference abstracts of RCTs[54, 55] were identified and included for extracting preliminary results despite their limited information.

3.7.3.1 Treatment of gonorrhoea in men and women (mixed population)

3 RCTs[52, 54, 55] were included that evaluated treatment of gonorrhoea in a mixed population of men and women. An overview of the number cured and the corresponding grading profiles are presented in Appendix 8.2 and 9.3.

Dual therapy for uncomplicated urogenital, pharyngeal or rectal gonorrhoea

Gentamicin + azithromycin versus gemifloxacin + azithromycin

Kirkcaldy et al.[52] conducted a randomised, multisite, open-label, noncomparative trial in 5 outpatient sexually transmitted disease clinic sites in Alabama, California, Maryland, and Pennsylvania. While the primary outcome was microbiological cure of urogenital infections (negative follow-up culture) at 10–17 days after treatment among 401 participants in the per protocol population, results were also reported for patients with pharyngeal infections (25 patients) and with rectal infection (1 patient). According to the randomisation, 202 participants received gentamicin 240 mg IM and azithromycin 2 g orally, and 199 participants received gemifloxacin 320 mg orally and azithromycin 2 g orally. Both treatments are non-cephalosporin-based regimens.

The majority of participants were men with only 10% women enrolled. The evidence suggested that there was no difference in number cured with urogenital infections (100% vs 95.5%; RR 1.01; 95% CI (0.99 to 1.02), low quality), pharyngeal infections (100% vs 100%; RR 1; 95% CI (0.86 to 1.17); low quality) or rectal infections (100% vs 100%; RR 1; 95% CI (0.43 to 2.31), very low quality).

Due to the very small sample size of patients with rectal and pharyngeal infections, no firm conclusion can be drawn for these sites.

The evidence suggested that gentamicin and azithromycin may provide a benefit in reduced nausea compared to gemifloxacin and azithromycin (27.7% vs 37.2%; RR 0.75; 95% CI (0.56 to 0.99), very low quality).

However, there was no difference in the adverse events vomiting (7.4% vs 5.0%), abdominal pain (7.4% vs 10.6%), diarrhoea (19.3% vs 23.1%), fatigue (2.0% vs 3.0%), dizziness (3.5% vs 3.5%), tendon disorder/tendonitis (0.5% vs 1.5%) and injection site pain (1.0% vs 0%) (1 study, very low quality).

Antimicrobial susceptibility of pre-treatment *N. gonorrhoea* isolates was reported using per protocol analysis (n=421). The percentage of isolates at or above minimum inhibitory concentration breakpoint was reported as: Azithromycin=0.5%, Cefixime=1.4%, Ceftriaxone=1.2%, Gemifloxacin=17.1%, Gentamicin=0%, Ciprofloxacin=24.5%, Penicillin=23%, Tetracycline=24.2% (1 study, very serious risk of bias).

Compliance was not reported.

Gentamicin + azithromycin versus Ceftriaxone + azithromycin

One blinded, two-arm, multicentre, noninferiority randomised trial[54] conducted in 13 outpatient sexual health clinics in England aimed to evaluate the effectiveness of dual therapy for patients with gonorrhoea. According to the study protocol,[104] patients were eligible for the trial if they had received a positive diagnosis in the last 4 weeks of uncomplicated, untreated genital, pharyngeal and/or rectal gonorrhoea. Diagnosis was based on a positive Gram-stained smear on microscopy, or a positive NAAT. The primary outcome was clearance of *N. gonorrhoea* at all infected sites by a negative NAAT, 2 weeks post treatment. Secondary outcomes include among others clinical resolution of symptoms and frequency of adverse events. The recruitment of patients and the collection of data are finished but up to now (May 2018), only preliminary results are published as conference abstract.

A total of 720 participants (presumed mixed population as not reported) evaluated gonorrhoea treatment with ceftriaxone 500 mg IM and azithromycin 1 g compared to gentamicin 240 mg IM and azithromycin 1 g. The evidence suggested that there was a benefit for ceftriaxone and azithromycin in number cured (based on NAAT) compared to gentamicin and azithromycin (98% vs 91%, low quality evidence). The same beneficial effect is reported for all anatomical sites: genital (98% vs 94%), pharynx (96% vs 80%) and rectum (98% vs 90%). The study reported that there was similar frequency of side effects between the treatment groups but figures were not provided.

Compliance and antimicrobial resistance were not reported.

Single therapy for uncomplicated urogenital gonorrhoea

ETX0914 vs Ceftriaxone

A phase II trial was conducted in the USA[55] to evaluate the effectiveness of ETX0914, a novel spiropyrimidinetrione antibiotic that unlike any marketed antibiotic, inhibits deoxyribonucleic acid biosynthesis by accumulation of double strand cleavages. In this multi-centre phase II trial, ETX0914 was administered for treatment of uncomplicated urogenital (urethral/cervical) gonorrhoea in men and women.

Participants were randomised approximately 70:70:40 to receive either 2000 mg or 3000 mg ETX0914 orally or 500 mg ceftriaxone in a single intramuscular injection. A test-of-cure visit occurred at 6 to 8 days after treatment to evaluate microbiological cure by culture, clinical cure and safety. A follow-up safety visit also occurred after one month. The primary efficacy outcome measure was the microbiological cure rate for uncomplicated urogenital gonorrhoea at the test-of-cure visit.

A total of 179 participants (7% were women) were enrolled, randomised, and treated. At baseline, 141 (79%) had positive urogenital cultures for gonorrhoea (132 urethral and 9 cervical). In the per protocol population, microbiological cure was achieved in 48/49 (98%) participants in the ETX0914 2000 mg arm, in 47/47 (100%) in the ETX0914 3000 mg arm, and in 21/21 (100%) in the ceftriaxone arm. ETX0914 was well tolerated with only 21/179 (12%) participants reporting 20 mild AEs and 1 moderate AE. The most common ETX0914-related AEs were gastrointestinal.

Compliance and antimicrobial resistance were not reported.

3.7.3.2 Treatment of gonorrhoea in men

One RCT[56] was included that evaluated treatment of gonorrhoea in men. An overview of the number cured and the corresponding grading profiles are presented in Appendix 8.2 and 9.3.

Dual versus single treatment for urethral gonorrhoea

Ceftriaxone + azithromycin versus fosfomycin trometamol

Yuan et al.[56] conducted an open randomised controlled trial in men with any main complaints suggestive of uncomplicated gonococcal urethritis in Dujiangyan Medical Centre (China). For the study, a Gram stain of urethral secretions that demonstrates polymorphonuclear leukocytes with intracellular Gram-negative diplococci was considered diagnostic for infection with gonorrhoea. The primary outcomes involved clinical and microbiologic cure on days 7 and 14 after receipt of all the study medications.

A total of 126 men evaluated gonorrhoea treatment with fosfomycin trometamol (n=62; 3 g orally administered alone at days 1, 3 and 5) compared to ceftriaxone (250 mg intramuscularly) plus azithromycin (1 g orally) (n=64). The evidence suggested that there was no difference in number cured (96.8% vs 95.3%; RR 0.98; 95% (CI 0.92 to 1.06), low quality) or any of the adverse events nausea (8.3% vs 4.9%), diarrhoea (11.7% vs 9.8%), abdominal pain (5% vs 6.6%), fatigue (3.3% vs 3.3%) or dyspepsia (8.3% vs 4.9%)(1 study, very low quality).

Compliance and antimicrobial resistance were not reported.

3.7.3.3 Treatment of gonorrhoea in women

No studies were identified.

3.7.3.4 *Conclusions: Treatment of gonorrhea in men and women (mixed population)*

Number cured

Urogenital infections

Dual treatment:

The evidence suggested no difference in number of urogenital infections cured between gemifloxacin and azithromycin compared to gentamicin and azithromycin.

The evidence suggested a benefit for ceftriaxone and azithromycin in increased number cured compared to gentamicin and azithromycin.

Single treatment:

The evidence suggested no difference in number cured between a new molecule tested in phase II trial ETX0914 (2000 mg) or ETX0914 (3000 mg) compared to ceftriaxone.

Rectal and pharyngeal infections:

Dual treatment:

The evidence, based on very low number of infections, suggested no difference in number of rectal and pharyngeal infections cured between gemifloxacin and azithromycin compared to gentamicin and azithromycin.

The evidence suggested a benefit for ceftriaxone and azithromycin in increased number cured compared to gentamicin and azithromycin.

Single treatment:

No evidence.

Adverse events

Dual treatment:

Gastrointestinal individual adverse events were reported up to 23% of patients treated. The evidence suggested no difference in adverse events regarding vomiting, abdominal pain, diarrhoea, fatigue, dizziness, tendon disorder/tendonitis and injection site pain reported for gentamicin and azithromycin compared to gemifloxacin and azithromycin, except for a small increase in nausea reported with gemifloxacin and azithromycin group. Gastrointestinal adverse events may limit routine use of both dual therapies.

Similar number of side effects reported between ceftriaxone and azithromycin compared to gentamicin and azithromycin (actual figures not reported).

Single treatment:

11.7% adverse events reported across ETX0914 and ceftriaxone groups with gastrointestinal events being the most common for the ETX0914 intervention.

3.7.3.5 *Conclusions: Men*

Number cured

Urogenital infections

Dual versus single treatment:

The evidence suggested no difference in number cured between ceftriaxone and azithromycin versus fosfomyc**in.**

Rectal and pharyngeal infections

No evidence.

Adverse events

Dual versus single treatment:

The evidence suggested no difference in adverse events nausea, diarrhoea, abdominal pain, fatigue, or dyspepsia between ceftriaxone and azithromycin compared to fosfomycin.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	There is low quality evidence for benefits and harms of dual therapy compared to single therapy, but due to emerging resistance to single therapies and lack of local surveillance data in most regions, dual therapy is favoured over single therapy. **Clinical evidence for dual therapy:** • Ceftriaxone and azithromycin: The evidence shows that dual treatment with ceftriaxone and azithromycin is effective for urogenital, pharyngeal, and rectal gonorrhoea (95% cure and higher) in men and women. • Gentamicin and azithromycin: The evidence shows that dual treatment is effective for urogenital (94-100%) but less effective for pharyngeal (80%) and rectal (90%) gonorrhoea in men and women. • Gemifloxacin and azithromycin: The evidence shows the treatment to be effective for urogenital gonorrhoea in men and women. Evidence is lacking for pharyngeal and rectal gonorrhoea. **Clinical evidence for single therapy:** • Fosfomycin is effective at treating urogenital gonorrhoea in men with urethritis**.** Gastrointestinal adverse events are common for all three dual therapies but do not compromise effectiveness owing to a low severity. The resistance data for Belgium showed low but increasing resistance to ceftriaxone between 2014 and 2017 with the latest result showing 0.34% of isolates being resistant. Azithromycin resistance is stable at 5% of isolates being resistant. The WHO guidance states that 'due to emerging resistance to single therapies and lack of local surveillance data in most regions, dual therapy is favoured over single therapy'. Dual therapy versus single therapy: On the basis of experience with other microbial species that have developed antimicrobial resistance rapidly, a theoretical basis exists for combination therapy using two antimicrobials with different mechanisms of action (e.g., a cephalosporin plus azithromycin) to improve treatment efficacy and potentially slow the emergence and spread of resistance to cephalosporins (CDC). This said, there is no evidence that in the case of gonorrhoea, dual therapy impedes the emergence of resistance over single therapy. **Dosage of molecules:** *This information was provided by Jørgen Skov Jensen (Gonorrhoea Guideline Editor, IUSTI 2012), 12.06.2018* • Ceftriaxone: A lot of discussions emerged during the development of the IUSTI guideline regarding the optimal dosage of Ceftriaxone, some members advocating that evidence from RCTs have to guide the recommendations and others insisting that at times of rapid changes in AMR levels, the results of RCTs are often obsolete at the time of publication. Ceftriaxone comes in 1g vials in many settings.

So, to avoid wasting a part of the vial in areas with a low prevalence of gonorrhoea, practitioners (including in Belgium) prefer to inject 1g of ceftriaxone (or use the content of one vial to treat the patient and his/her partner (500 mg each).

- Azithromycin: A lot of discussions emerged during the development of the IUSTI guideline regarding the optimal dosage (1g vs 2g). The most important reason for the 2g dose was the fact that in treatment trials, 1g was shown to lead to failure and 2g less so. According to the PI of the IUSTI guideline, the CDC and WHO guidelines were more focused on treating simultaneous chlamydia than on actually trying to knock out CTX resistant strains. Another reason was the idea that 1g selected more resistance for *Mycoplasma genitalium* compared to the 2g.

Adherence and side effects

- To maximise adherence with recommended therapies and reduce complications and transmission, medication for gonococcal infection should be provided on site and directly observed.
- If medications are not available when treatment is indicated, linkage to an STI treatment facility should be provided for same-day treatment**.**
- Gastrointestinal side effects are very high and a number of patients do not tolerate 2g and will throw up before absorption has occurred when 2g azithromycin is administered. This has to be monitored.

The GDG proposed the same combination treatment regimens for all patients except pregnant women, for the following reasons:

- Currently, the combination treatment and the dosages are appropriate to avoid resistance;
- Same treatment for vaginal, urethral, pharyngeal and anal infections;
- The treatment is in line with the European guideline and the following Belgian guidelines: BCFI 2018; BAPCOC 2012 first line; BAPCOC hospital care 2017; Agentschap zorg en gezondheid 2017; Domus Medica 2017; and Ghapro 2014
- A consistent treatment across the line is easy to remember and to communicate.

For pregnant women, the GDG proposed single treatment with ceftriaxone for the following reasons:

- Currently, there have been no cases of resistance in the treatment of pregnant women;
- Same treatment for vaginal, urethral, pharyngeal and anal infections;
- The treatment is in line with the European guideline and the guideline published by the Agentschap zorg en gezondheid 2017

Report from the scientific validation of this guideline:

- The validators reported that in their respective countries, the Netherlands and France, the local guidelines advices monotherapy of ceftriaxone for gonorrhoea infection.
- The United Kingdom recently changed the treatment of uncomplicated ano-genital and pharyngeal infections in adults from dual therapy to monotherapy. The dose of ceftriaxone was increased to 1g IM.[105]
- **The validators** understood the process and decision making for the dual treatment of the GDG. Nevertheless, the validators pointed out that AMR should be followed closely in Belgium and the treatment strategy adapted if AMR increases. For ceftriaxone the AMR is low at 0.3% (most recent results); if the AMR increases the dosage of 500mg can be increased to 1g as is the case in the Netherlands and UK. The AMR of azithromycin was between 2% and 8% in the last 10 years. The use of azithromycin at a lower dose of 1g is more likely to select for resistance.[106, 107] The validators pointed out that: Azithromycin is the first line treatment for non-gonococcal urethritis often caused by chlamydia but also ***Mycoplasma genitalium***. Mycoplasma macrolide (azithromycin) resistance unfortunately is becoming widespread with high rates been reported e.g. Australia macrolide resistance of 50% or higher.[107, 108] **The treatment option for *M genitalium*** are therefore becoming limited. The STI communities are advocating against syndromic management and for point-of-care tests to identify ***M genitalium*** and gonorrhoea with determination of resistance profiles.[108]

Quality of evidence	Update literature search: 2 RCTs with low to very low quality evidence; 2 RCTs (conference abstracts) with low quality evidence.
Costs (resource allocation)	Spectinomycin (Trobicine) and cefixime are not available in Belgium. Spectinomycin was taken of the market in 2016 and is no longer available. The recommendation on the BCFI website is no longer relevant (communicated by BCFI-CBIP on May 31st 2018). A prescriber can have the spectinomycin imported on a patient named basis but reimbursement is not applicable in this case. The cost of ceftriaxone and azithromycin and reimbursement is summarized in Table 37. WHO statement on cost: 'Dual therapy is currently being used in some settings and it appears to be acceptable, and the costs compared to effectiveness are not greater than single therapy. A test of cure to ensure eradication of infection and/or identify emerging resistance adds an extra cost to the care package of the patient. For the individual patient with persisting symptoms, this strategy may be beneficial and improve care. A test of cure can also contribute to the public health and detect changes in resistance levels to antibiotics and inform public health surveillance on the correct antibiotic treatment.
Patients values and preferences	WHO guideline: No studies were found that assessed patient values and preferences, acceptability, equity or feasibility specific to gonococcal infections. Some health-care providers are, in practice, averse to providing injections, and additional labour time and costs are associated with IM administration. There is probably no variability in the values people place on the outcomes. However, IM injection may be less desirable among patients than oral administration, and dual therapy is acceptable to patients based on current use.

Table 37 – Gonorrhoea medication prices and availability in Belgium

Antibiotic	BCFI		Public price (in €)	Out-of-pocket payment (in €)
Ceftriaxone	Mylan	Hospital 1 x 1 g IM (powder + solvent)	4	4
	Mylan	Hospital 1 x 1 g IM (powder + solvent)	44	44
	Fresenius Kabi	10 X 1 g IM	56.61 (BCFI recommended 'cheap')	11.90
	Sandoz	Hospital 10 x 1 g IM	47	47
	Rocephine	1 x 1 g with 3.5 ml solvent	10.72	2.47 or 1.63
Azithromycine	Sandoz	6x500 mg & 3x500mg	14.20 & 9.46	6.66 & 3.39
	Teva	6x500 mg & 3x500mg	14.20 & 9.46	6.66 & 3.39
	EG	6x500 mg & 3x500mg	14.42 & 9.46	6.81 & 3.39
	Mylan	6x500 mg	14.68	6.99
	Apotex	6x500 mg & 3x500mg	14.69 & 9.67	7.00 & 3.54
	Zitromax	3x500mg	9.46	3.39

3.7.4 Recommendation for treatment of gonorrhoea in women and men including young people

Treatment of gonorrhoea in women and men including young people	Strength of Recommendation	Level of Evidence
First line therapy for uncomplicated gonorrhoea of the urethra, cervix, rectum and pharynx in sexually active non-pregnant women and men including young people is recommended as follows: **Dual therapy:** Ceftriaxone 500 mg IM in a single dose AND azithromycin 2 g orally for all cases in a single dose	Weak	Very low

3.7.5 Treatment of gonorrhea: Good practice statements

Treatment of gonorrhoea: Good practice statements
Belgian resistance data should determine the choice of therapy for gonorrhoea
As dual therapy, ceftriaxone and azithromycin should be administered together on the same day, preferably simultaneously and under direct observation.
Azithromycin tablets may be taken with or without food but gastrointestinal side-effects can be less if taken after food.

3.8 Treatment of gonorrhoea: Treatment choice in pregnant women

3.8.1 Recommendations from international guidelines

Source and target population	Recommendation for 1st line	Remarks	Alternatives
UNCOMPLICATED GENITAL AND ANORECTAL GONOCOCCAL INFECTIONS			
WHO 2016[22] Target population: adults, adolescents (10–19 years of age), people living with HIV, and key populations, including sex workers, MSM and transgender persons **including pregnant women.**	***Dual therapy (one of the following)*** • ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose • cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose ***Single therapy (one of the following, based on recent local resistance data confirming susceptibility to the antimicrobial)*** • ceftriaxone 250 mg IM as a single dose • cefixime 400 mg orally as a single dose • spectinomycin 2 g IM as a single dose. (Conditional recommendation, low quality evidence).	Alternative single-medicine therapies, such as gentamicin or kanamycin, have not been suggested due to lack of surveillance data.	
IUSTI 2012[2] **Pregnant women and during breastfeeding**	Ceftriaxone 500 mg intramuscularly as a single dose (Ib; A)	The safety of azithromycin in pregnancy has not been confirmed but clinical experience indicates that it may be safely used. It should only be used under medical supervision if the expected benefit to the mother is thought to be greater than the possible risk to the foetus. Azithromycin passes into breast milk and is not recommended while breast feeding. Pregnant and breastfeeding women should not be treated with fluoroquinolone or tetracycline antimicrobials	Spectinomycin 2 g intramuscularly as a single dose

UNCOMPLICATED OROPHARYNGEAL GONOCOCCAL INFECTIONS		
WHO 2016[22] Target population: adults, adolescents (10–19 years of age), people living with HIV, and key populations, including sex workers, MSM and transgender persons **including pregnant women**.	***Dual therapy (one of the following)*** • ceftriaxone 250 mg IM as a single dose PLUS azithromycin 1 g orally as a single dose • cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose Single therapy (based on recent local resistance data confirming susceptibility to the antimicrobial) • ceftriaxone 250 mg IM as single dose. (Conditional recommendation, very low quality evidence).	Treatment failures have been observed after single therapy for gonococcal oropharyngeal infections and therefore dual therapy is suggested over single therapy.

3.8.2 Recommendations from national guides

Table 38 – Recommendations from national guides – Molecules and dosages for pregnant women

	Pregnant women
Guide	**First choice**
BVIKM/SBIMC[a]	Ceftriaxone 500 mg OR 1 g AND Azithromycin 2 g

Note. [a] *BVIKM: Belgische vereniging voor infectiologie en klinische microbiologie; SBIMC: Société belge d'infectiologie et de microbiologie clinique*

3.8.3 Additional literature search: Treatment of gonorrhoea in pregnant women

One systematic review[50] was identified that included two randomised controlled trials[51, 53] evaluating single therapy for gonorrhoea treatment in pregnant women. These two RCTs randomised 514 pregnant women (347 women analysed) at a mean gestational age of 22 weeks. Both trials were conducted in the outpatient department of the same two hospitals in the USA between 1993 and 2001, and had a follow-up of 14 days. One trial compared ceftriaxone (125 mg, intramuscular) with cefixime (400 mg, oral);[53] the other trial had three arms, and assessed ceftriaxone (250 mg, intramuscular) versus either amoxicillin (3 g, oral) plus probenecid (1 g, oral) or spectinomycin (2 g, intramuscular).[51] No more recent study was identified for this population group. Neither of the trials reported on two of this review's primary maternal outcomes: incidence of obstetric complications (miscarriage, premature rupture of membranes, preterm delivery, or foetal death), or disseminated gonococcal infection, or on the incidence of neonatorum ophthalmia in the neonates. An overview of the number cured and the corresponding grading profiles are presented in Appendix 8.2 and 9.3.

3.8.3.1 Ceftriaxone (125 mg IM) versus cefixime (400 mg orally)

One RCT[53] comprising 95 pregnant women evaluated gonorrhoea treatment with ceftriaxone 125 mg intramuscularly compared to cefixime 400 mg orally. The evidence suggested that there was no difference in number cured overall (95.3% vs 96.2%; RR 0.99; 95% CI (0.91 to 1.08), number cured of cervical infections (95% vs 95.7%; RR 0.99; 95% CI (0.9 to 1.09)), rectal infections (100% vs 100%; RR 1; 95% CI (0.9 to 1.11)), 1 study, low quality) or pharyngeal infections (100% vs 100%; RR 1; 95% CI (0.73 to 1.37), 1 study, very low quality). The evidence suggested that cefixime may provide a benefit in fewer cases of minor abnormalities in babies (11.3% vs 16.7%; RR 1.48; 95% CI (0.60 to 3.62)) and hyperbilirubinemia in infants (0% vs 8.3%; OR 8.19; 95% CI (1.38 to 48.71)) compared to ceftriaxone (1 study, very low quality). Compliance and antimicrobial resistance were not reported.

3.8.3.2 Ceftriaxone (250 mg IM) versus spectinomycin (2 g IM)

One RCT[51] comprising 252 pregnant women evaluated gonorrhoea treatment with ceftriaxone 250 mg intramuscularly compared to spectinomycin 2 g intramuscularly. There was a third arm amoxicillin that was not included as penicillin is no longer advised due to resistance. The evidence suggested that there was no difference in number cured (overall, cervix or rectal infections) (1 study, low quality), minor or major congenital malformations (1 study, very low quality). The evidence suggested that there may be a small benefit for ceftriaxone with more cured pharyngeal infections compared to spectinomycin (1 study, very low quality). Compliance and antimicrobial resistance were not reported.

3.8.3.3 Conclusions: Pregnant women

Number cured

Urogenital infections

Single treatment:

The evidence suggested no difference in number cured between ceftriaxone compared to cefixime.

The evidence suggested no difference in number cured between ceftriaxone and spectinomycin.

Rectal infections

Single treatment:

The evidence suggested no difference in number cured between ceftriaxone compared to cefixime.

The evidence suggested no difference in number cured between ceftriaxone and spectinomycin.

Pharyngeal infections

Single treatment:

The evidence suggested no difference in number cured between ceftriaxone compared to cefixime.

The evidence suggested that there may be a benefit for ceftriaxone with more cured pharyngeal infections compared to spectinomycin.

Adverse events

The evidence suggested that cefixime may provide a benefit in fewer cases of minor abnormalities in babies and hyperbilirubinemia in infants compared to ceftriaxone.

3.8.3.4 Contra-indications and complications of gonorrhoea medication for pregnant women

Therapeutic option	Use during pregnancy
Ceftriaxone	US FDA Category B: Animal studies have failed to reveal evidence of embryotoxicity, foetotoxicity, or teratogenicity. This drug crosses the placenta. There are no controlled data in human pregnancy. This drug should be used during pregnancy only if clearly needed and the benefit outweighs the risk.
Gentamicine	US FDA Category D: Animal studies have failed to reveal evidence of teratogenicity; however, nephrotoxicity occurred in foetal rats. There are no controlled data in human pregnancy. If gentamicin is used during pregnancy or if the woman becomes pregnant during therapy, she should be advised of the potential risk to the foetus. Aminoglycosides can cause foetal harm when given to pregnant women. Aminoglycosides cross the placenta and there are reports of foetal eight cranial nerve toxicity with permanent bilateral deafness after in utero exposure to streptomycin. Serious side effects to mother, foetus, or new-born have not been reported in pregnant women treated with other aminoglycosides. Safety of gentamicin has not been established; potential benefit should outweigh the potential risk.
Azithromycin	US FDA category B: Animal models given moderately maternally toxic doses have failed to reveal evidence of foetal -or teratogenicity. There are no controlled data in human pregnancy. Use is not recommended unless clearly needed. *BCFI:* This drug should be used during pregnancy only if clearly needed and the benefit outweighs the risk.
Cefixime	US FDA category B: Animal studies failed to reveal evidence of foetal harm. There are no controlled data in human pregnancy. Use is only recommended when benefit outweighs risk.
Fosfomycin	US FDA category B: Animal studies have revealed evidence of foetotoxicity but only at doses which also resulted in maternal toxicity. When administered as the sodium salt (IM injection), fosfomycin crosses the placental barrier in humans. There are no controlled data in human pregnancy. A single 3g oral dose of fosfomycin tromethamine was given (in water) to 153 pregnant women with bacteriuria. Infecting organisms were eradicated in 96% of patients, with recurrence rate of 3% after 25 to 30 days. Minimal maternal side effects occurred and no serious adverse foetal effects were documented. The trimester in which the drug was administered was not reported. This drug should be used during pregnancy only if clearly needed.
Gemifloxacin	US FDA category C: Animal reproduction studies have shown an adverse effect on the foetus (foetotoxicity, delayed foetal growth, human foetal bone formation) and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Because safer alternatives are generally available, some experts consider fluoroquinolones contraindicated during pregnancy, especially during the first trimester.
Spectinomycin	US FDA category B: Since safety in pregnancy had not been established, spectinomycin should be used in pregnant women only if the need outweighs any possible risk to the foetus.
Amoxicillin	US FDA category B: Animal studies have failed to reveal evidence of teratogenicity, impaired fertility, or foetal harm. The effects during labour and delivery are unknown. There are no controlled data in human pregnancy. Use is recommended only if clearly needed and the benefit outweighs the risk.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	The clinical evidence is limited and dated from before the era of gonorrhoea resistance. The therapeutic options are limited for pregnant women as the drugs are category B US FDA: drugs should be used during pregnancy only if clearly needed and the benefit outweighs the risk. Other items as for adult men and women apply. Other items as for adult men and women apply.
Quality of evidence	Additional literature search: 2 RCTs with low to very low quality.
Costs (resource allocation)	Other items as for adult men and women.
Patients values and preferences	Preference for oral treatment over IM.

3.8.4 *Recommendation for treatment of gonorrhoea in pregnant women*

Treatment of gonorrhoea in pregnant women	Strength of Recommendation	Level of Evidence
First line therapy for uncomplicated gonorrhoea of the urethra, cervix, rectum and pharynx in pregnant women is recommended as follows: **Single therapy:** Ceftriaxone 500 mg IM in a single dose for all cases	Weak	Very low

3.8.5 *Treatment of gonorrhoea in pregnant women: Good practice statements*

Treatment of gonorrhoea in pregnant women: Good practice statements
Belgian resistance data should determine the choice of therapy for gonorrhoea.
The diagnosis of gonorrhoea in pregnant women should be communicated with the gynaecologist to ensure follow-up of adverse events of treatment and complications of infection for the mother as well as the foetus or neonate.
Pregnant women found to have gonococcal infection should be treated immediately, and should have a test of cure 4 weeks after treatment.
Pregnant women found to have gonococcal infection should be retested during the third trimester to prevent maternal postnatal complications and gonococcal infection in the neonate.

3.9 Treatment of gonorrhoea: Treatment choice in people with an allergy to cephalosporin

3.9.1 Background cephalosporin allergy

Cephalosporins can cause IgE-mediated allergic reactions characterized by urticaria, angioedema, bronchospasm, and anaphylactic shock, typically an immediate reaction within 1 hour. Cephalosporin hypersensitivity does not seem to be a class hypersensitivity as it is probably due to allergy mediated by the molecular side chains of the main molecule. Skin testing for penicillin, ampicillin, amoxicillin, and 11 cephalosporins in 102 patients with allergy showed to cross-reactivity occurring within a group of cephalosporins that have a common side chain (cefuroxime, ceftriaxone, cefotaxime, cefepime, and ceftazidime) and within a group consisting of ampicillin and two aminocephalosporins (cefaclor and cephalexin). Patients who were allergic to cephalosporins in one group generally tolerated drugs from the other group. Cefazolin typically was tolerated by patients with allergies to cephalosporins in either group.[109]

Patients with penicillin allergies usually can tolerate all cephalosporins, and patients with cephalosporin allergies usually can tolerate a cephalosporin with a different side chain. Rarely, a patient with a history of penicillin or cephalosporin allergy might react to another cephalosporin because of its β-lactam ring or other unexplained metabolites, so performing skin testing or a graded challenge is sometimes performed prior to administering a cephalosporin to such a patient.

3.9.2 Recommendations from international guidelines

Source and target population	Recommendation for 1st line	Remarks	Alternatives
GENITAL, ANORECTAL, AND OROPHARYNGEAL GONOCOCCAL INFECTIONS IN CASE OF CEPHALOSPORIN RESISTANCE			
IUSTI 2012[2]	• Ceftriaxone 1 g intramuscularly as a single dose together with azithromycin 2 g oral single dose (IV; C). • Gentamicin* 240 mg intramuscularly as a single dose together with azithromycin 2 g oral as single dose (IV; C).		*This combination is currently under clinical study and may be valuable if infection persists after treatment with ceftriaxone.

*Note. * Gentamicin has been successfully used in Malawi, Africa for many years (mainly in syndromic management administered together with doxycycline) and high in vitro susceptibility in Europe has been proven. However, randomised, quality-assured clinical trials need to confirm the efficacy of this treatment regimen.*

3.9.3 Recommendations from national guides

Table 39 – Recommendations from national guides – Molecules and dosages for people with an allergy to cephalosporin

	People with an allergy to cephalosporin
BAPCOC 2012 (first line)	Spectinomycine 2 g AND Azithromycin 2 g
Agentschap zorg en gezondheid 2017	Azithromycine 2 g AND Gentamycine 240 mg IM.*

**Allergy for type 1 beta-lactam allergy, defined as anaphylactic shock and angioedema; not for pharyngeal infection.*

3.9.4 Additional literature search: Treatment of gonorrhoea in people with an allergy to cephalosporin

There was no study identified comparing gonorrhoeal treatments for people with severe cephalosporin allergy.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Known cases of cephalosporin allergy should be referred to the second line. As discussed for adult women and men.
Quality of evidence	Update literature search: No evidence was identified.
Costs (resource allocation)	As discussed for adult women and men.
Patients values and preferences	As discussed for adult women and men.

3.9.5 Treatment of gonorrhoea in people with an allergy to cephalosporin: Good practice statement

Treatment of gonorrhoea in people with an allergy to cephalosporin: Good practice statement
In case of allergy to penicillin/cephalosporin, patients with gonorrhoea of the urethra, cervix, rectum, or pharynx have to be referred to the second line to receive the most adequate treatment.

3.9.6 Recommendations for treatment of chlamydia and gonorrhoea co-infection

Treatment of a co-infection gonorrhoea and chlamydia	Strength of Recommendations	Level of Evidence
Urogenital or oropharyngeal infection		
Ceftriaxone 500 mg IM in a single dose AND azithromycine 2 g orally in a single dose	Weak	Very low
Anorectal infection		
Ceftriaxone 500 mg IM in a single dose AND doxycycline 100 mg twice a day orally for 7 days	Weak	Very low
Anorectal infection in HIV positive men with unknown status of LGV		
Anorectal LGV infection		
Ceftriaxone 500 mg IM in a single dose AND doxycycline 100 mg twice a day orally for 21 days	Weak	Very low
Pregnant women		
Ceftriaxone 500 mg IM in a single dose AND azithromycine 1 g orally in a single dose	Weak	Very low

3.10 Test of cure and follow-up for gonorrhoea

3.10.1 Recommendations from international guidelines

The following two different approaches to performing a test of cure are applied on an international level:

- The first approach applied by the CDC and WHO, considers **the individual who fails therapy**. The recommendation is to take a culture from a person failing therapy for antimicrobial susceptibility testing, and to start subsequent treatment according to the results.
- In several European countries and Canada, the approach is to perform a universal test of cure of **all positive patients**.[2, 110] The reasoning is based on the epidemiology of gonorrhoea. Antimicrobial resistant (AMR) gonorrhoea is more common in Europe compared to the US. Of note is that breakpoints for resistance have been lower in Europe compared to US. Multidrug-resistant (MDR) gonorrhoea organisms (resistant to ceftriaxone and cefixime, penicillin, azithromycin, doxycycline, and ciprofloxacin) have been detected for example in the United Kingdom. The public health implications of the MDR gonorrhoea becoming more widespread are serious. A surveillance system based on universal test of cure is therefore advocated by the countries applying this approach.[2, 110]

Nevertheless, both approaches advocate for extra caution with pharyngeal infections.

- Treatment failure has been hypothesised to be linked to extragenital infections serving as a reservoir and promoting sustained transmission.
- Pharyngeal gonorrhoea is more difficult to treat probably due to lower drug levels leading to resistance development.
- Further, the infection with gonorrhoea in the pharynx is thought to contribute to the evolution of antimicrobial resistance. The gonococcus mingles with commensal *Neisseria* species in the pharynx, acquiring genetic material through transformation.

Table 40 – When and how to perform a test of cure for gonorrhoea – Definitions from international guidelines

Source		Recommendation for 1st line
IUSTI 2012[2]	WHO	In all gonorrhoea cases to ensure eradication of infection and identify emerging resistance (IV, C)
	WHEN and HOW	Persistence of symptoms: culture 3-7 days after treatment completion; if culture negative supplement with NAAT 7 days later (IV, C) Asymptomatic: NAAT two weeks after treatment completion; if positive perform culture with antibiotic susceptibility testing before starting further treatment (IV, C)
CDC 2015[12]	WHO	Routine test of cure for persons diagnosed with urogenital or rectal gonorrhoea who are treated with the 1st line or alternative regimen is NOT recommended. Test of cure is recommended in the following situations: • In case of suspicion of treatment failure with the recommended regimen • Expected treatment failure: use of alternative treatment regimen for pharyngeal infection
	WHEN and HOW	Culture or NAAT can be used for test of cure. If a NAAT test of cure is positive, every effort should be made to obtain confirmatory culture before retreatment, and all positive test of cure cultures should undergo antimicrobial susceptibility testing. A. For treatment failure: test of cure at the relevant anatomic site 7–14 days after retreatment. Culture is the recommended test for test of cure, preferably with simultaneous nucleic acid amplification test (NAAT). Antimicrobial susceptibility testing should be performed if *N. gonorrhoeae* is isolated. B. NAATs, test of cure should be performed 14 days after treatment in the setting of pharyngeal infections treated with the alternative regimen and 7–14 days after retreatment in the setting of suspected treatment failure.
British Association for Sexual Health and HIV 2011[96]	WHO	A test of cure (TOC) is now recommended in all cases (IV; C) Whenever universal not feasible, then the following patients should be prioritized: • persisting symptoms or signs • pharyngeal infection (all treatments are less effective at eradicating pharyngeal infection) • treatment with anything other than the first-line recommendations • pregnant women
	WHEN and HOW	Culture should be performed at least 72 hours after completion of treatment for persisting symptoms. If asymptomatic, test with NAAT's where available followed by culture if positive. Test two weeks after completion of antibiotic therapy.
USPSTF 2014[25]	WHO	Pregnant women diagnosed with a gonococcal infection in the first trimester
	HOW	To retest 3 months after treatment.

Other information regarding drug resistance gonorrhoea in Australia[111]: A gonorrhoea patient who recently travelled in Southeast and East Asia should have samples from all potentially infected sites pre-treatment: NAAT and culture with antimicrobial susceptibility when symptomatic. Culture is taken for all cases infected in Southeast and East Asia.

3.10.2 Recommendations from national guides

Table 41 – Recommendations from national guides – Test of cure

Source		Recommendation for 1st line
Zorg en Gezondheid 2017	WHO	Persistence of symptoms after treatment
	HOW	Culture with antimicrobial susceptibility testing. NAAT two weeks after treatment completion
Domus Medica 2017	WHO	• Oropharyngeal infection • Expected problem with therapy compliance • Persistent symptoms • Alternative therapy
	HOW	NAAT test two weeks or later after treatment for any indication For persisting symptoms or alternative therapy: culture with antimicrobial susceptibility testing from 3-7 days after treatment
Ghapro 2014	WHO	• Oropharyngeal infection • Persistent symptoms
	HOW	Culture with antimicrobial susceptibility testing (condition culture sample and transport are important)

3.10.3 Recommendations regarding a test of cure for gonorrhoea

Test of cure for gonorrhoea	Strength of Recommendations	Level of Evidence
Test of cure should be performed optionally in gonorrhoea cases to ensure eradication of infection and identify emerging resistance. Test of cure should be performed in case of: • Suspicion of treatment failure • Pharyngeal infection • When a different regimen is used than indicated in this guideline (e.g. monotherapy) • In case of treatment of a co-infection with chlamydia • Pregnant women • After travelling to Southeast and East Asia	Weak	Very low
Scheme of the test of cure If persistence of symptoms: culture with antibiotic susceptibility of all the relevant anatomic sites 3-7 days after treatment completion; if culture negative supplement with NAAT 14 days after completion of treatment; If asymptomatic: NAAT four weeks after treatment completion; if positive perform culture with antibiotic susceptibility testing of all the relevant anatomic sites before referral to second line and starting further treatment.	Weak	Very low

3.10.4 Recommendations regarding testing frequency for gonorrhoea

Testing frequency for gonorrhoea	Strength of Recommendations	Level of Evidence
Repeat testing interval every 3 to 12 months (same for other STIs) for asymptomatic patients with high risk sexual behaviour or at increased risk for gonorrhoea:		
1. Sex worker of any gender	Weak	Very low
2. MSM with high risk sexual behaviour • unprotected sexual contacts in non-exclusively monogamous relationships • who are on PrEP • with a recent HIV diagnosis • with a STI diagnosis in the past	Weak	Very low
3. Adolescents and young people up to the age of 29 years who continue to have unprotected oral, anal or vaginal intercourse in non-exclusively monogamous relationships	Weak	Very low
4. Heterosexual patient who continues to have unprotected oral, anal or vaginal intercourse in non-exclusively monogamous relationships	Weak	Very low

3.11 Notification of gonorrhoea

3.11.1 Recommendations from international guidelines

Source	Recommendation for 1st line
ALL CASES	
IUSTI 2012[2]	Infections with *N. gonorrhoea* should be notified to local, regional and national authorities as mandated by statute. The ECDC is responsible for the European Union-wide surveillance of communicable diseases including gonorrhoea.

3.11.2 *Mandatory notification of gonorrhoea*

All cases of infections by *N. gonorrhoea* have to be notified in Brussels and Flanders using one of the three channels offered to healthcare practitioners to notify an infectious disease (phone, mail or website).

3.12 Assessment of risk for syphilis

Table 42 – Risk factors and risk groups for syphilis infection: overview of international guidelines

Source	Recommendation for 1st line
US Preventive Services Task Force 2016[29] Asymptomatic, nonpregnant adults and adolescents who are at increased risk for syphilis infection	The USPSTF recommends screening for syphilis in persons who are at increased risk for infection: • MSM • men and women living with HIV • those with previous syphilis infection • an infected sexual partner • more than 4 sex partners in the preceding year Factors associated with increased prevalence that clinicians should consider include: • history of incarceration • history of commercial sex work • certain racial/ethnic groups • and being a male younger than 29 years
IUSTI 2014[11]	The following groups at higher risk of syphilis: • all patients who are newly diagnosed with STI • persons with HIV • persons with hepatitis B • persons with hepatitis C • persons suspected of early neurosyphilis (i.e. unexplained sudden visual loss, unexplained sudden deafness or meningitis) • persons who engage in sexual behaviour that puts them at higher risk: o men who have sex with men o sex workers and all those individuals at higher risk of acquiring STIs Screening tests should also be offered to all attendees at 'sexual health clinics'.

BASHH 2015[6]	Six and 12 weeks after a single 'high risk' exposure: • unprotected oral, anal or vaginal intercourse with homosexual man • multiple partners • anonymous sex in saunas and other venues • commercial sex worker • sex partner linked with a country where the prevalence of syphilis is known to be high
CDC 2015[10]	• young women: <25 years, and ≥25 years if at increased risk • pregnant women • men in high prevalence settings • MSM • persons with HIV

3.13 Diagnosis of syphilis

3.13.1 Diagnostic tests and testing approach for syphilis

Syphilis is a sexually transmitted or congenital acquired systemic human disease caused by the spirochete bacterium *Treponema pallidum*. This infection might remain asymptomatic and latent for many years. During early infection an ulcer appears which can be sampled for diagnosis with direct detection methods. In a later stadium serological tests are used. An overview of the diagnostic tests is proposed in Table 43.

3.13.1.1 Direct detection methods

PCR can be used to directly detect *T. pallidum* and can be useful for ulcers e.g. of the genital, pharyngeal and oral mucosa. PCR has a high sensitivity on ulcer material (low sensitivity on blood of below 40%). Expertise to perform dark-field microscopy (high specificity, low sensitivity) to visualise *T. pallidum* is available at the Institute of Tropical Medicine; samples have to be taken on site. This method is obsolete and hardly ever used. Overall, PCRs for the detection of *Treponema pallidum* seem to be specific when using genital ulcer material. However, we lack evidence confirming that in oral and anal ulcer specimens the commensal treponema are not occasionally amplified. In addition, the morphology of the treponemes is identical and a distinguishment cannot be made using dark field microscopy. This can result in biological false positives. An advantage of the direct detection methods is that it allows an early diagnosis of syphilis prior to a serologic response (see tests below). Caution should be taken with PCR tests for *T. pallidum* as they are currently not internationally approved and a strict laboratory validation protocol with the use of controls has to be present for good quality.[112, 113]

3.13.1.2 Serological tests

There are 2 different types of serological tests based on the type of antigen the antibodies are directed against.

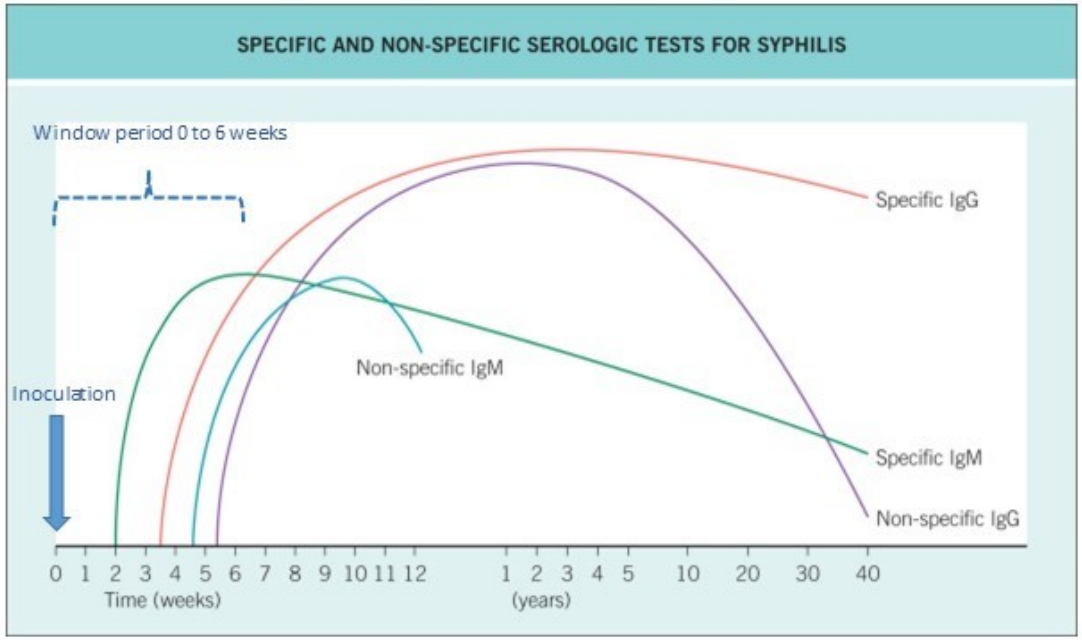
Treponemal tests detect antibodies against *T. pallidum* proteins. Examples are the

- Fluorescent treponemal antibody absorption test (FTA-Abs)
- Treponema Pallidum Particle Agglutination test (TPPA)
- Enzyme Immunoassay (EIA)
- Chemiluminescence Immunoassay (CIA)
- Multiplex flow immuno test (MFI)
- Microbead immunoassay (MBIA)
- Rapid tests (e.g. immunochromatographic assay)
- IgM enzyme immuno and line immunoassay

Non-treponemal tests detect antibodies (a mixture of IgG and IgM) directed against lipoidal antigens, and damaged host cells (mixture of cardiolipin, lecithin, and cholesterol). The main two tests are: the rapid plasma reagin (RPR) test which is mostly used internationally and in Belgium; the Venereal Disease Research Laboratory (VDRL) test which is less used but performs well on cerebrospinal fluid. Both tests are used to confirm the infection and determine whether the disease is an active or an old infection.[114]

The antibody patterns over time are presented in Figure 5. Incubation is typically 3 to 6 weeks. Early syphilis is defined as within one year by the ECDC, and late thereafter (ending with the development of tertiary disease). For a diagnosis of *Treponema pallidum* the result of one test does not suffice. A person with a positive serological test should be investigated and treated as for syphilis as a precautionary measure unless previously adequately treated syphilis is documented. Algorithms that combine both the results of treponemal and non-treponemal serological tests are used to define an active infection and its stage (primary, secondary or tertiary). It can be difficult to define the exact stage of the infection solely on the basis of laboratory tests and especially when a patient is asymptomatic. Guidance from the clinician by adding the clinical information to the laboratory request, is necessary to make a laboratory diagnosis. Syphilis is relatively easy to detect if combined serological tests are used. The serological tests are commonly supplemented with validated and quality assured PCR tests in very early syphilis cases.

Figure 5 – Treponemal infection antibody patterns over time



Source: Personal communication Prof Henry de Vries

Table 43 – Types of tests for syphilis

Test	Use	Characteristics
Direct detection methods		
PCR	Detection of genetic material of bacteria in chancre and ulcer (early stage), blood, or cerebrospinal fluid (late stage)	Positive test result indicates presence of *T. pallidum* nucleic acid
Microscopic or darkfield exam: Sample from chancre is placed on a slide and examined with a special microscope	Now obsolete: Diagnostic of syphilis in primary stage	Syphilis is diagnosed if bacteria are seen.
Antibody tests		

***Treponemal Antibody Tests:* (mostly IgG and IgM combined)** ***T. pallidum* particle agglutination (TPPA) (manual)** **Enzyme immunoassay (EIA)** **Chemiluminescence immunoassay (CIA)** **Multiplex flow immunoassay (MFI)** **Rapid point of care (POC) tests** **IgM enzyme immune and line-immune tests** **Fluorescent treponemal antibody absorbed (FTA-ABS) (time-consuming, obsolete)**	Screening Confirmation of a positive treponemal test Confirmation of a positive non-treponemal antibody test Detection of very early acute infections (IgM) To differentiate active from past infection, a positive treponemal result must be combined with a non-treponemal antibody test Use of POC tests for global elimination of congenital syphilis and mother to child transmission at the field level (same visit treatment in remote settings); not recommended in Europe	Highly specific Treponemal antibodies remain positive for life, even after treatment Mostly automated (less labour intense) (EIA & CIA) False positive reactions due to autoimmune disease or the presence of commensal treponemas can happen
Non-treponemal Antibody Tests: **Venereal Disease Research Laboratory (VDRL), rapid plasma reagin (RPR)**	Differentiation between active and past infection (RPR) Evaluation of disease activity (RPR) Guidance of treatment (RPR) Detection of neurosyphilis (VDRL approved for cerebrospinal fluid testing)	Detect a mixture of IgG and IgM qualitatively (flocculation) and quantitatively (by serum dilution: a fourfold change or more in reactivity is significant). Become positive 6 weeks after infection or 10-15 days after the occurrence of primary chancre Titre correlates with disease activity Remains positive with low titre in late stage disease Highly sensitive except for the first weeks of infection and in the late (tertiary) stage Non-treponemal antibodies generally disappear with treatment after 3 years Non-treponemal antibodies can become negative spontaneously without treatment. Labour intensive (manual not automatizable); laboratory material is cheap

Source: table created by KCE, information retrieved from Agency for Healthcare Research and Quality (2016), IUSTI (2014) and personal communication (Dr T. Crucitti, Syphilis Reference Centre, ITM, Belgium)

3.13.1.3 Testing algorithms

For the diagnosis of syphilis a blood sample is typically sent to the laboratory together with the clinical background and reason for testing. The final result (positive, negative) should be based on a laboratory testing algorithm that makes use of more than one test performed on the same sample. Several algorithms are in place that combine serological tests, i.e. a traditional, a reverse, an updated reverse, and a hybrid algorithm.

The traditional syphilis screening algorithm consists of an initial screening using a non-treponemal test, followed by confirmation of reactive results using a treponemal test (Figure 6).

The reverse sequence syphilis screening (RSSS) algorithm adopts a reverse sequence of tests, starting with a treponemal test as a screening test, followed by confirmatory testing of reactive samples with a non-treponemal test (Figure 7). By performing the initial screening with a fully automated, treponemal test, the RSSS has clear advantages, particularly in reducing the workflow challenge faced by reference laboratories performing a huge number of tests every month. However, in settings with a low prevalence of syphilis, using a treponemal test as the first step leads to many false reactive results. Nevertheless, for laboratories, the number of required manual confirmatory tests will significantly decrease.[115] Non-treponemal tests typically become non-reactive 12-24 months after treatment of early disease; so, a negative non-treponemal confirmatory test does not definitively indicate that the original treponemal result was falsely reactive. A treponemal reactive/non-treponemal non-reactive result suggests that the patient is unlikely to have active disease, but such result does not rule out acute infection or late/latent disease. To definitely conclude to a false reactive initial treponemal result, the RSSS algorithm requires to perform a second treponemal assay, different from the initial screening treponemal assay. If this second treponemal assay is reactive, the initial positive result is confirmed, and a clinical evaluation could allow to stage the infection. If the second treponemal assay is non-reactive, this suggests that the initial treponemal test was likely a false screening result and the patient is unlikely to have been exposed to syphilis.[115] In STI clinics, where higher prevalence of syphilis is reported, or in developing countries with limited access to testing, the likelihood of encountering both early syphilis and late/latent syphilis (LSS) increases. The RSSS algorithm is likely to detect more cases of untreated disease in these settings, but cases of treated disease will also be identified, increasing follow-up costs and need to manage personal and social impact associated with identification of past infection.[115]

ECDC advocates a flexible approach with combinations of the serological options and supports an alternative strategy, the updated reverse algorithm. In this 'updated' reverse algorithm a treponemal-specific test is used, followed by a second treponemal test and then followed by a non-treponemal test (). The second treponemal test increases specificity and reduces the false positive results encountered on the automated machines. Detailed information can be found in the IUSTI guideline.[11] In case of a negative non-treponemal test (after two positive treponemal tests), treponemal IgM is tested to detect a very early infection even in asymptomatic patients.

The CDC continues to recommend the traditional algorithm but acknowledges the use of treponemal immunoassays as a first approach.[10] Given the options and to allow flexibility, the choice of test remained open in KCE report 248 'What are the recommended clinical assessments and screening test during pregnancy' from 2015.[116]

Another algorithm that is used in case of high clinical suspicion (anogenital ulcer, repeat infection) is a hybrid approach. A treponemal and non-treponemal test are performed in parallel on the same sample.[11] To resolve discordant results, a second treponemal test is performed in a second stage (Figure 8). If there is high suspicion (e.g. ulcer presence), treatment will be started even when the non-treponemal test is negative.

Figure 6 – Traditional algorithm for syphilis diagnosis

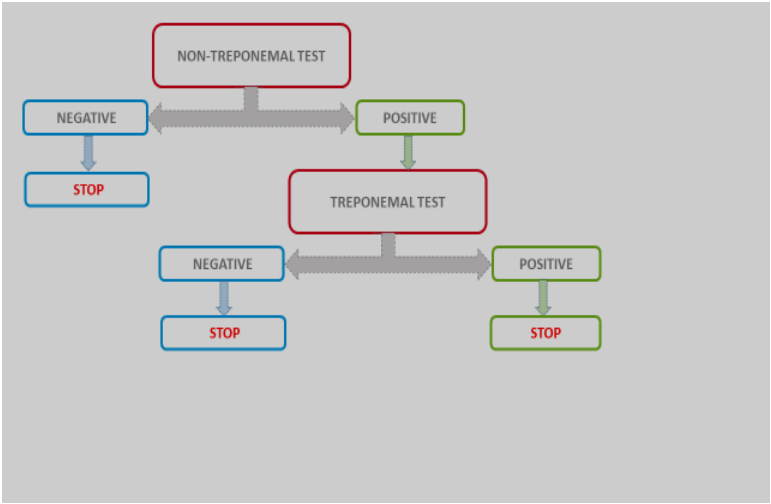


Figure 7 – Updated reverse algorithm for syphilis diagnosis

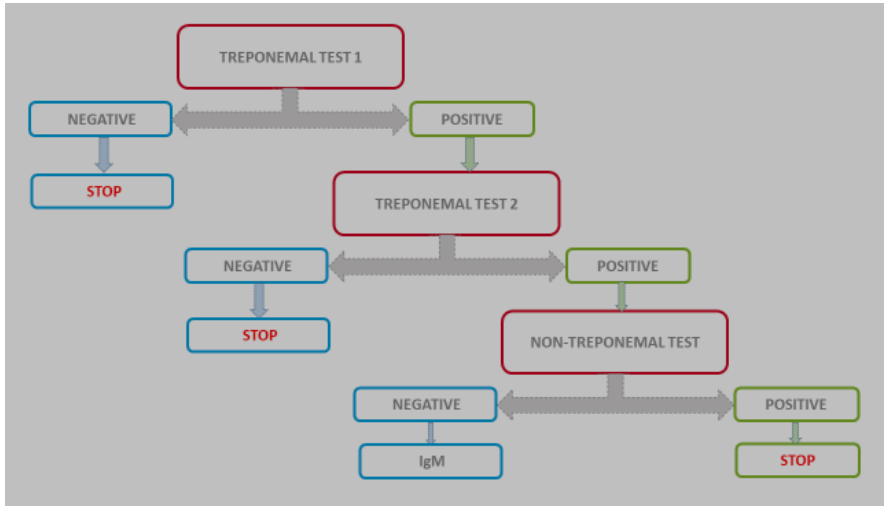
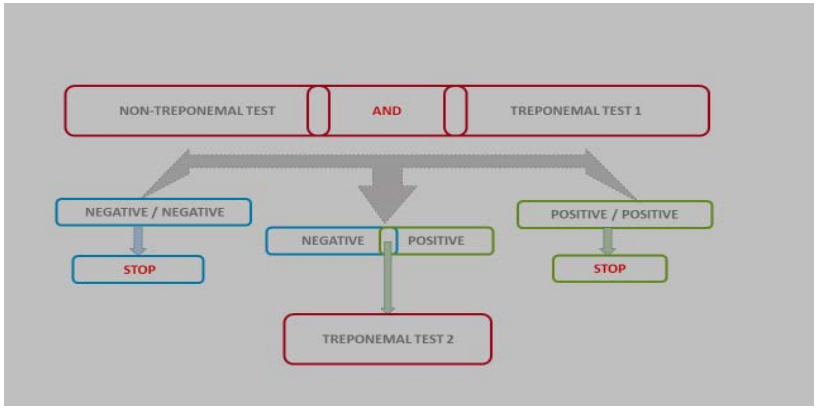


Figure 8 – Hybrid algorithm for syphilis diagnosis



Source figures: created by KCE, based on Tong 2014[117] and IUSTI 2014[11] (with the kind support of Dr T. Crucitti)

3.13.1.4 Point of care (POC) tests

Syphilis bedside tests are currently used for the diagnosis in settings where direct results are of high importance for earlier treatment: resource-limited settings for prevention of congenital syphilis (WHO strategy for worldwide elimination of congenital syphilis); settings with poor access to regular laboratory testing; populations with poor access to testing (e.g. migrants). For Belgium, these scenarios are less common. Currently, the performance of the rapid syphilis tests is poor and a rapid test (based on a single treponemal test) will result in false positives and overtreatment as treponemal antibodies stay positive for life. New tests are in development, often in combination with HIV testing. The performance characteristics for HIV are prioritised with poor syphilis performance as a consequence.

In 2016, the WHO STI POCT initiative published a target product profile for syphilis POC tests. According to this profile, a syphilis POC test should have a sensitivity of at least 80% and a specificity >90%. These standards ensure acceptable positive predictive value (PPV) and negative predictive value (NPV) and a major effect in terms of clinical utility in low-income, middle-income countries and, by extension, among hard-to-reach populations, where similar high rates of syphilis prevalence (3%–5%) have been reported[118] (see also http://www.who.int/reproductivehealth/topics/rtis/pocts/en/ and http://who.int/reproductivehealth/POTC-TPPs-2016.pdf?ua=1; accessed on September 1, 2018). WHO and the European guidelines advise against the use of the syphilis POC tests in low syphilis prevalence settings, such as Belgium, as performance is low and access to laboratory high performance test is not an issue.[118] The use of any POC test at clinical sites requires ongoing supervision by a reference laboratory, including provision of an external quality assurance programme.[114]

3.13.2 Recommendations from international and national guidelines

An overview of the conclusion of international guidelines is presented in Table 44. We summarized the recommendations on the target population for syphilis testing, the diagnostic tests and the testing approach that is used, the type of sample to be taken, and information on the time interval for syphilis testing.

Table 44 – Conclusions and recommendations for diagnostic of syphilis from selected clinical guidelines

Source	Recommendation for 1st line
Target population (see also section below which samples for specific groups)	
WHO 2017[28] Pregnant women	WHO recommends screening all pregnant women for syphilis during the first antenatal care visit (Strong recommendation, moderate-quality evidence)
BASHH 2015[6] Pregnant women	All pregnant women should have syphilis serology at their first antenatal clinic visit, and if risk of syphilis is recognised re-screening later in pregnancy should be offered (1A).
KCE 2015[116] Pregnant women	As treatment is favourable for the prognosis of both the mother and child, offer each pregnant woman to test for syphilis, in the beginning of pregnancy (or before) (Strong recommendation, moderate-quality evidence).
BASHH 2015[6] Sexually active people who are at increased risk for syphilis infection	Six and 12 weeks after a single 'high risk' exposure (unprotected oral, anal or vaginal intercourse with homosexual man, multiple partners, anonymous sex in saunas and other venues, commercial sex worker or sex partner linked with a country where the prevalence of syphilis is known to be high).

	In individuals at ongoing risk due to frequent 'high risk' exposures as defined above, screening as part of routine sexual health check-ups for all STIs including HIV and others is recommended, usually every three months and informed by sexual history. Two weeks after presentation in those with dark field or PCR negative ulcerative lesions that could be due to syphilis.
US Preventive Services Task Force 2016[29] Asymptomatic, nonpregnant adults and adolescents who are at increased risk for syphilis infection	Screening for syphilis infection is currently recommended for high-risk individuals, including those with previous syphilis infection, an infected sexual partner, HIV infection, or more than 4 sex partners in the preceding year.
IUSTI 2014[11]	Case finding: Routine tests for syphilis should be taken in all pregnant women, people donating blood, blood products or solid organs and the following groups at higher risk of syphilis: all patients who are newly diagnosed with STI; persons with HIV; patients with hepatitis B; patients with hepatitis C; patients suspected of early neurosyphilis (i.e. unexplained sudden visual loss, unexplained sudden deafness or meningitis); patients who engage in sexual behaviour that puts them at higher risk (e.g. men who have sex with men (MSM), sex workers and all those individuals at higher risk of acquiring STIs). Screening tests should also be offered to all attendees at dermatovenereology/genitourinary medicine (GUM)/STI clinics afterwards referred to as 'sexual health clinics'

Diagnostic tests and testing approaches

	Recommendations for 1st line	Remarks
WHO 2017[28] Pregnant women	• In settings with a high prevalence of syphilis (5% or greater), the WHO STI guideline suggests an on-site rapid syphilis test (RST) and, if positive, provision of a first dose of treatment and a rapid plasma reagin (RPR) test, and then, if the RPR test is positive, provision of treatment according to duration of syphilis (Strategy C). The WHO STI guideline suggests this sequence of tests and treatment rather than a single on-site RST (Strategy A) or a single on-site RPR test (Strategy B) (Conditional recommendation, low-quality evidence). • In settings with a low prevalence of syphilis (below 5%), the WHO STI guideline suggests a single on-site rapid syphilis test (RST) be used to screen pregnant women (Strategy A) rather than a single on-site rapid plasma reagin (RPR) test (Strategy B) (Conditional recommendation, low-quality evidence). • In settings with low coverage of syphilis screening and treatment for pregnant women, high loss to follow-up of pregnant women, or limited laboratory capacity, the WHO STI guideline suggests on-site tests (Strategies A, B and C) rather than the standard off-site laboratory-based screening and treatment strategy (Conditional recommendation, low-quality evidence).	These recommendations do not apply to countries that can provide appropriate/high-quality laboratory-based screening and treatment strategies. However, in some settings there may be challenges providing such strategies and/or a sequence of tests. When resources do not permit the use of a sequence of tests, a single on-site rapid syphilis test (RST) (Strategy A) is suggested to ensure greater screening coverage despite the number of pregnant women who will be over-treated due to the high rate of false-positive results.

US Preventive Services Task Force 2016[29] Asymptomatic, nonpregnant adults and adolescents who are at increased risk for syphilis infection	Screening for syphilis infection is a 2-step process involving an initial nontreponemal test (Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR] test) followed by a confirmatory treponemal antibody detection test (fluorescent treponemal antibody absorption [FTA-ABS] or Treponema pallidum particle agglutination [TPPA] test).	A reverse sequence screening algorithm has been developed in which an automated treponemal test (such as enzyme-linked, chemiluminescence, or multiplex flow immunoassays) is performed first, followed by a nontreponemal test. If the test results are discordant in the reverse sequence algorithm, a second treponemal test (preferably using a different treponemal antibody) is performed. There is limited evidence on the accuracy of screening using the reverse sequence algorithm.
CDC 2015[10]	The CDC recommends the use of the traditional RPR-based screening algorithm.	
BASHH 2015[6]	***Demonstration of T. pallidum from lesions or infected lymph nodes***: • Where appropriate expertise and equipment are available, perform dark ground microscopy on possible chancres (2A); • T. pallidum testing by PCR is appropriate on lesions where the organism may be expected to be located (1A). ***Serological test for syphilis:*** • An EIA/CLIA, preferably detecting both IgM and IgG is the screening test of choice (1B). • Positive screening tests should be confirmed with a different treponemal test (not the FTA-abs) and a second specimen for confirmatory testing obtained (1B). • A quantitative RPR or VDRL should be performed when screening tests are positive (1A). • Repeat negative serological tests for syphilis (STS): o At six and 12 weeks after an isolated episode which is high risk for exposure to syphilis, o At two weeks after possible chancres that are dark-ground and/or PCR negative are observed (1B). • Those with possible gummatous, neurological or cardiovascular symptoms or signs require examination and further evaluation by appropriate specialists (1C).	
IUSTI 2014[11]	Primary screening test(s) A. Treponema Test (TT), by preference an automatized EIA/ CIA, is particularly suitable for automated high-throughput screening of asymptomatic populations and blood/plasma donors: • persons with previous successful treatment	A. able to detect very early syphilis A. can result in a high number of false positive tests (low positive predictive value) in low-prevalence populations B. it can miss very early syphilis more often than TT

	• untreated syphilis B. Non-Treponemal Test (NTT) (ideally quantitative to detect prozone phenomenon in infectious syphilis), is still recommended in the USA and some European countries. In this algorithm, only active (infectious) syphilis is detected. C. Both a TT and a NTT. This algorithm is wise in case of suspicion of very early syphilis (recent chancre, contacts of syphilis cases etc.) Confirmation test on the same serum if any screening test is positive: A. Another TT of a different type AND a quantitative NT If this second TT is positive B. A TT C. NTT quantitatively	Although confirmation of a positive TT and ruling out a false positive test may be important for counselling, notification and have a psychological impact, it has limited impact on treatment.
Which sample by stage of syphilis		
CDC 2015 **BASHH 2015[6]** **IUSTI 2014**	• Smears from lesions or chancres if lesions or chancres are visible in the mouth, the anal and/or the genital area (primary syphilis) • Venous blood sample for all syphilis stages (early/latent/late syphilis) Cerebrospinal fluid (CSF) for secondary and tertiary syphilis	
Testing intervals		
US Preventive Services Task Force 2016[29] Asymptomatic, nonpregnant adults and adolescents who are at increased risk for syphilis infection	The optimal screening frequency for persons who are at increased risk for syphilis infection is not well established. MSM or persons living with HIV may benefit from more frequent screening. Initial studies suggest that detection of syphilis infection in MSM or persons living with HIV improves when screening is performed **every 3 months** compared with annually.	
BASHH 2015[6] Sexually active people who are at increased risk for syphilis infection	In individuals at ongoing risk due to frequent 'high risk' exposures, screening as part of routine sexual health check-ups for all STIs including HIV and others is recommended, usually **every 3 months** and informed by sexual history. Two weeks after presentation in those with dark field or PCR negative ulcerative lesions that could be due to syphilis.	

3.13.3 Additional literature search: Diagnosis of syphilis

Two research questions were addressed:

1. What is the accuracy of currently used strategies (e.g. sequence of tests) for detecting syphilis infection?
2. What are the diagnostic tests of choice for diagnosis of syphilis in primary care?

3.13.3.1 Accuracy of testing strategies

Two observational studies were retrieved that compared traditional testing strategies with reverse testing strategies in men and women.[58, 64]

One of the studies[58] was a prospective cohort study that compared reverse testing to traditional testing algorithm on 1000 sera samples collected in a low prevalence population in a US laboratory.

- Reverse testing consisted of a multiplex flow immunoassay (MFI) followed by RPR on positive samples. TPPA was performed on MFI positive but RPR negative samples. A positive testing examination was defined as MFI positive with RPR or TPPA positive test.
- The traditional algorithm used RPR, followed by TPPA. A positive test was defined as a positive RPR and TPPA.

The number of reactive samples using the reverse algorithm were 15/1000 (1.5%) compared to 4/1000 (0.4%) using the traditional algorithm [Moderate quality evidence]. The four reactive samples in the traditional algorithm were also selected from reverse algorithm giving 11 discordant patients. These patients medical records were reviewed and the authors deducted that 3 patients had a history of past, successfully treated syphilis and were not retreated. 2 patients were reactive by MFI and TPPA but not reactive by RPR and were diagnosed with possible latent syphilis and treated. The remaining 6 patients were reactive by MFI but nonreactive by RPR and TPPA and diagnosed as falsely reactive.

The other study was a retrospective time-series study[64] that tested all serum samples submitted for syphilis testing from centres in the greater Toronto Area (Canada). The study compared outcomes from the traditional algorithm (used from August 1998- July 2005) with the reverse algorithm (used from August 2005-July 2008).

The number of samples confirmed positive using the reverse algorithm was 1.98% compared to 0.46% using the traditional algorithm [Low quality evidence].

It was noted that 69.6% of reverse algorithms positives were RPR negative. The reverse algorithm resulted in an increased diagnosis of syphilis that was not detected under screening with RPR.

Table 45 – GRADE profile: Diagnostic strategy for syphilis diagnosis

Study characteristics			Quality Assessment					Summary of findings Positive samples (%)		
No. of studies	**Design**	**No.**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Reverse algorithm**	**Traditional algorithm**	**Quality**
Reverse versus traditional algorithm - women and men										
Reactive samples										
1	Diagnostic cohort study	1000	Serious risk of bias[1]	Not applicable	No serious indirectness	Not applicable	None	15/1000 1.50%	4/1000 0.40%	MODERATE
Samples confirmed positive										
1	Time-series	3 092 938	Very serious risk of bias[1]	Not applicable	No serious indirectness	Not applicable	None	20 533/1 037 025 1.98%	9457/2 055 913 0.46%	LOW

[1] *Risk of bias was assessed using the QUADAS-2 checklist. If there was one criterion with a high risk of bias the study was considered to have a serious risk of bias. If there were two or more criteria with a high risk of bias the study was considered to have a very serious risk of bias. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias. The evidence was downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

3.13.3.2 Diagnostic accuracy of tests for syphilis in men and women (mixed population)

Seven studies were identified that reported the diagnostic accuracy of diagnostic tests for syphilis in men and women.[59-63, 65, 66] The results are presented by type of test: polymerase chain reaction (PCR) assay, enzyme immunoassay (EIA) and rapid point of care (POC) tests.

An overview of the diagnostic accuracy and its corresponding grading profiles are presented in Appendix 8.3 and 9.4.

Table 46 – List of assay names

Assay name	Short name
PCR	
TaqMan real-time PCR assay targeting the polA gene of Treponema pallidum	TpPCR
EIA antibodies	
Trep-Check IgG treponemal enzyme immunoassay (EIA) (Phoenix Bio-Tech corp)	EIA IgG
Trep-Sure IgM/IgG Sensitive EIA (Trinity Biotech, Jamestown NY)	EIA IgM/IgG
POC	
SD Bioline HIV-syphilis duo test (Abbott)	SD HIV-syp (trep)
Chembio DPP HIV-syphilis assay	Chembio DPP HIV-syp (trep)
Chembio Dual Path Platform (DPP) syphilis screen and confirm assay	
Chembio DPP HIV-HCV-syphilis assay	Chembio DPP HIV-HCV-syp (trep)

PCR tests on swabs and biopsies

One study[63] conducted in Australia compared TpPCR testing on swabs and biopsies from men and women. Authors aimed to develop a robust, sensitive, and specific real-time PCR assay to directly detect the presence of pathogenic *Treponema pallidum* in swabs and biopsy specimens from genital and mucosal ulcers, placental specimens, and cerebrospinal fluid. In this study, samples were collected from Melbourne clinics with a high caseload of MSM, HIV patients, and other patients with high rates of STIs and referred to The Victorian Infectious Diseases Reference Laboratory (VIDRL) that acts as the state reference laboratory for syphilis serology.

- Of the 660 specimens from 590 patients tested, positive TpPCR results were obtained for 55 specimens from 51 patients. HIV-infected males had the highest rate of positive results.
- Directly compared with serology, TpPCR showed 95% agreement, with a sensitivity of 80.4% and a specificity of 98.4% compared with serology for the detection of early syphilis [Very low quality evidence].

EIA tests on serum samples

Two studies compared EIA IgG and EIA IgM/IgG testing on serum samples from men and women.[65, 66]

One study[12] was conducted in Canada to evaluate the Trep-Chek IgG EIA for its performance against a battery of screening and confirmatory tests. The Trep-Chek IgG EIA is used for the qualitative detection of human IgG antibodies to *T. pallidum*. This study was carried out using serum specimens submitted from provinces on the basis of their need for either confirmation of local test results or for further testing to evaluate patient/clinical status. There were no prior selection criteria for sample inclusion nor was there any effort to include samples from certain patient categories (such as primary or secondary syphilis, or samples with false-positive syphilis serology on the basis of conventional testing).

- The EIA IgG had a sensitivity of 85% and specificity of 96% [Very low quality evidence]. The relatively poor sensitivity of 85.3% may be due to the small number of syphilis-positive cases included in this study (29/604). Moreover, the Trep-Chek IgG EIA detects only IgG antibodies,

inherently missing early syphilis cases as the primary immune response is driven by IgM specific antibodies.

The second study[14] was conducted in the USA (San Francisco) to evaluate the TREP-SURE EIA (TS-EIA) compared to the VDRL test. The TS-EIA is capable of detecting both IgG and IgM. Blood specimens were collected from patients presenting to San Francisco municipal STD clinic. The VDRL testing population at this clinic is 69.3% MSM, 16.6% of the tested population is HIV-positive and 9.4% have had a documented case of early syphilis.

- The EIA IgM/IgG had a sensitivity of 98% and specificity of 99% [Low quality evidence]. While the TS-EIA was less sensitive than the VDRL for testing this population, the TS-EIA was far more specific than the VDRL. The high prevalence of HIV infection in the population may have affected the results and cause false-positive VDRL results.

POC tests on blood and serum samples

Four studies compared Chembio DPP syp (non-trep+ trep), HIV-syp (trep) and HIV-HCV-syphilis tests on serum and blood samples from men and women.[59-62]

Chembio DPP syp (non-trep + trep): Two studies[59, 60] reported diagnostic accuracy of the Chembio DPP syp (non-trep + trep) test comparing the treponemal line of the test to a treponemal reference standard (TPPA) and the non-treponemal line to a non-treponemal reference standard (RPR).

The first study[4] was conducted in Atlanta (USA), where authors used 1 601 banked serum samples to compare results obtained by the dual test with results obtained using a quantitative RPR test and the TPPA assay.

- The treponemal test had a sensitivity of 97% and specificity of 95% [Low quality evidence] while the non-treponemal test had a sensitivity of 89% and specificity of 99% [Low quality evidence]. Compared to the RPR test, the reactive concordance of the dual test nontreponemal line was 98.4% when the RPR titers of sera were ≥1:2 and the nonreactive concordance was 98.6%. Compared to the TPPA assay, the reactive and nonreactive concordances of the treponemal line were 96.5% and 95.5%, respectively.

The second study evaluated the performance of three rapid POC tests in an at-risk population seeking HIV and STI testing at a testing center in Long Beach, California (USA).[7] A total of 948 whole blood specimens were analyzed to evaluate the performance of the Dual Path Platform (DPP) Syphilis Screen & Confirm, DPP HIV-Syphilis, and DPP HIV-HCV-Syphilis rapid tests. For syphilis, the gold-standard comparisons were TPPA and RPR.

- The treponemal test had a sensitivity of 53% and specificity of 99% in blood samples [Very low quality evidence] while the non-treponemal test had a sensitivity of 48% and specificity of 99% in blood samples [Very low quality evidence].
- When the treponemal and non-treponemal lines results were combined on blood samples, the sensitivity increased to 90% and the specificity to 99.6% [Very low quality evidence].

Dual tests for HIV and syphilis: Three studies compared a dual HIV/syphilis test on blood and serum samples on men and women.[60-62]

One study[61] conducted in the USA tested a POC test, the SD Bioline HIV/Syphilis DUO rapid test, a compact, qualitative, cartridge-based immunochromatographic assay, which uses finger-stick whole blood, plasma, or sera to detect antibodies to HIV-1/2 and *T. pallidum*, and delivers results in 15–20 min. A total of 394 specimens were tested for syphilis.

- For syphilis: When compared to RPR, SD-DUO sensitivity and specificity were 85.7% and 96.8%, respectively [Very low quality evidence]. When compared to TPPA, SD-DUO sensitivity and specificity were 69.7% and 99.7%, respectively [Very low quality evidence].
- For HIV: When compared to health clinic results, SD-DUO sensitivity and specificity were 91.7% and 99.5%, respectively. After discrepant testing with the tie-breaker test, both HIV false positives and the HIV false negative were resolved in favour of the SD-DUO test, yielding an 'adjusted' sensitivity and specificity of 100%.

Two studies reported on the Chembio DPP HIV-syp (trep) test one using blood sample and the other using serum samples.[60, 62]

The first study recruited participants from a center in California (USA).[7] A total of 948 whole blood specimens were analyzed to evaluate the performance of the Dual Path Platform (DPP) Syphilis Screen & Confirm, DPP HIV-Syphilis, and DPP HIV-HCV-Syphilis rapid tests. The gold-standard comparisons were TPPA, RPR and HIV-1/2 EIA. This study[60] using blood samples started testing for HIV and then syphilis (order 1) and then switched the order half way through to test for syphilis first and then HIV (order 2).

- For syphilis: Order 1 had a sensitivity of 46% and specificity of 100% and order 2 had a sensitivity of 47% and specificity of 99% [Very low quality evidence].
- For HIV: Order 1 had a sensitivity of 100% and a specificity of 100%, respectively. After the change in configuration, the sensitivity was 95.7% and the specificity was 99.7%.

The second study[62] evaluated the performance of the Chembio Dual Path Platform (DPP®) HIV-Syphilis Assay in 990 serum samples from the Georgia Public Health Laboratory in Atlanta, Georgia (USA). HIV reference testing combined third-generation Enzyme Immunoassay and Western Blot, whereas reference testing for syphilis was conducted by the *Treponema pallidum* passive particle agglutination method and the TrepSure assay. Sensitivity and specificity of the DPP assay on this panel were assessed by comparing results with the HIV and syphilis reference testing algorithms.

- For syphilis, sensitivity was 98.8% and specificity was 99.4% [Low quality evidence].
- For HIV, sensitivity was 99.8% and specificity was 98.4% [Low quality evidence].
- Of the 348 co-infected sera, 344 (98.9%) were detected accurately by the DPP assay, but 11 specimens had false-positive results (9 HIV and 2 syphilis) due to weak reactivity

Chembio DPP HIV-HCV-syp (trep): One study recruited participants from a testing center in California (USA).[7] A total of 948 whole blood specimens were analyzed to evaluate the performance of the DPP HIV-HCV-Syphilis rapid tests. The gold-standard comparisons were TPPA, RPR, HCV enzyme immunoassay (EIA), and HIV-1/2 EIA.

- For syphilis: The study reported a sensitivity of 44% and specificity of 99% using blood samples [Low quality evidence].
- For HIV: The study reported a sensitivity of 100% and specificity of 99.9% using blood samples [Low quality evidence].
- For HCV: The study reported a sensitivity of 91.8% and specificity of 99.3% using blood samples [Low quality evidence].

Conclusions on the diagnostic accuracy of tests for syphilis in men and women

In Table 47, an overview is presented on the retrieved diagnostic accuracy of tests in men and women.

Table 47 – Overview of the diagnostic accuracy to detect syphilis in men and women

WOMEN AND MEN	Blood	Serum	Swabs and biopsies
TpPCR	/	/	Sens: 80% Spec: 98% PPV: 91%
EIA IgG	/	Sens: 85% Spec: 96% PPV: 54%	/
EIA IgM/IgG	/	Sens: 98% Spec: 99% PPV: 98%	/
Chembio DPP syp (non-trep + trep) Treponemal line	Sens: 53% Spec: 99% PPV: 85%	Sens: 97% Spec: 95% PPV: 97%	/
Chembio DPP syp (non-trep + trep) Non-treponemal line	Sens: 48% Spec: 99% PPV: 58%	Sens: 89% Spec: 99% PPV: 99%	/
Chembio DPP syp (non-trep + trep) combined	Sens: 90% Spec: 100% PPV: NR	/	/
SD HIV-syp (trep)	/	Sens: 70% Spec: 100% PPV: 96%	/
Chembio DPP HIV-syp (trep)	Sens: 46-47% Spec: 99-100% PPV: 93%	Sens 99% Spec: 99% PPV: 100%	/

Chembio DPP HIV-HCV-syp (trep)	Sens: 44% Spec: 99% PPV: 90%	/	/

In the GRADE profiles (Table 48), an overview is presented of the number of studies per comparison, the quality assessment and the summary of findings. These considerations served as a basis for the formulation of the conclusions and the recommendations.

Table 48 – GRADE profiles: Diagnostic tests for syphilis in women and men, by assay

Study characteristics			Quality Assessment					Summary of findings Range % (95% CI)		
No. of studies	**Design**	**No.**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sensitivity (%)**	**Specificity (%)**	**Quality**
PCR tests										
Women and men – TpPCR using swabs and biopsies (prevalence 16.9%)										
1	Diagnostic cohort studies	301	Very serious risk of bias[1]	Not applicable	No serious indirectness	Serious imprecision[3]	None	80 (67 to 90)	98 (96 to 100)	VERY LOW
EIA tests										
Women and men – EIA IgG using serum samples (prevalence 5.6%)										
1	Diagnostic cohort studies	604	Very serious risk of bias[1]	Not applicable	No serious indirectness	Serious imprecision[3]	None	85 (69 to 95)	96 (94 to 97)	VERY LOW
Women and men – EIA IgM/IgG using serum samples (prevalence 39.7%)										
1	Diagnostic cohort studies	674	Very serious risk of bias[1]	Not applicable	No serious indirectness	No serious imprecision	None	98 (96 to 99)	99 (97 to 100)	LOW
Chembio DPP syp (non-trep + trep) tests										
Women and men – treponemal test with TPPA as reference standard using serum samples (prevalence 52%)										

Study characteristics			Quality Assessment					Summary of findings Range % (95% CI)		Quality
No. of studies	Design	No.	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (%)	Specificity (%)	
1	Diagnostic cohort studies	1601	Very serious risk of bias[1]	Not applicable	No serious indirectness	No serious imprecision	None	97 (95 to 98)	95 (93 to 97)	LOW
Women and men – treponemal test with TPPA as reference standard using blood samples (prevalence 2.4%)										
1	Diagnostic cohort studies	765	Very serious risk of bias[1]	Not applicable	No serious indirectness	Serious imprecision[3]	None	53 (42 to 63)	99 (97 to 99)	VERY LOW
Women and men – non-treponemal test with RPR as reference standard using serum samples (prevalence 52%)										
1	Diagnostic cohort studies	1601	Very serious risk of bias[1]	Not applicable	No serious indirectness	No serious imprecision	None	89 (86 to 91)	99 (97 to 99)	LOW
Women and men – non-treponemal test with RPR as reference standard using blood samples (prevalence 2.4%)										
1	Diagnostic cohort studies	763	Very serious risk of bias[1]	Not applicable	No serious indirectness	Very serious imprecision[3]	None	48 (27 to 69)	99 (98 to 100)	VERY LOW
Women and men – combined treponemal and non-treponemal using blood samples (prevalence 2.4%)										
1	Diagnostic cohort studies	766	Very serious risk of bias[1]	Not applicable	No serious indirectness	Very serious imprecision[3]	None	90 (55 to 100)	100 (99 to 100)	VERY LOW

Point of Care – dual and triple tests										
Women and men – SD HIV-syp (trep) – using serum and plasma samples (prevalence 8.4%)										
1	Diagnostic cohort studies	394	Very serious risk of bias[1]	Not applicable	No serious indirectness	Serious imprecision[3]	None	70 (51 to 84)	100 (98 to 100)	VERY LOW
Women and men – Chembio DPP HIV-syp (trep) – using blood samples (prevalence 2.4%)										
1	Diagnostic cohort studies	920	Very serious risk of bias[1]	Not applicable	No serious indirectness	Serious imprecision[3]	None	Order 1: 46 (28 to 66) Order 2: 47 (36 to 59)	Order 1: 100 (98 to 100) Order 2: 99 (98 to 100)	VERY LOW
Women and men – Chembio DPP HIV-syp (trep) – using serum samples (prevalence 65.4%)										
1	Diagnostic cohort studies	990	Very serious risk of bias[1]	Not applicable	No serious indirectness	No serious imprecision	None	99 (98 to 99)	99 (98 to 100)	LOW
Women and men – Chembio DPP HIV-HCV-syp (trep) – using blood samples (prevalence 2.4%)										
1	Diagnostic cohort studies	881	Very serious risk of bias[1]	Not applicable	No serious indirectness	No serious imprecision	None	44 (34 to 54)	99 (99 to 100)	LOW

[1] Risk of bias was assessed using the QUADAS-2 checklist. If there was one criterion with a high risk of bias the study was considered to have a serious risk of bias. If there were two or more criteria with a high risk of bias the study was considered to have a very serious risk of bias. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias. The evidence was downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

[3] Imprecision was based on the range of point estimates or, if only one study contributed to the evidence, the 95% CI around the single study. As a general rule a variation of 0–20% was considered precise, 20–40% serious imprecision, and >40% very serious imprecision. Imprecision was assessed on the primary outcome measure for decision-making.

3.13.3.3 Diagnostic accuracy of tests for syphilis in MSM

PCR tests on swabs and biopsies

No evidence was identified that reported on PCR tests in MSM.

EIA tests on serum samples

No evidence was identified that reported on EIA tests in MSM.

POC tests on blood and serum samples

One study[67] prospectively recruited 289 asymptomatic MSM, potentially exposed to syphilis as a result of risky behaviours, in Verona, Italy. Authors reported the diagnostic accuracy of the Chembio DPP syp (non-trep + trep) test and the SD Syphilis 3.0 assay in MSM using blood and serum samples. This study did not report the crude data but provided a sensitivity and specificity from two different readers.

Chembio DPP syp (non-trep + trep):

The study reported the diagnostic accuracy of the Chembio DPP syp (non-trep + trep) test comparing the treponemal line of the test to a treponemal reference standard (TPPA) and the non-treponemal line to a non-treponemal reference standard (RPR) for blood and serum samples.

- The treponemal test using blood samples had a sensitivity of 65% and 69% (reader 1 and 2 respectively) and specificities of 100% (both readers) [Low quality evidence].
- The treponemal test using serum samples had a sensitivity of 58% and 64% and specificities of 100 and 99% (reader 1 and 2 respectively) [Low quality evidence].
- The non-treponemal test using blood samples had a sensitivity of 64% and specificity of 100% in both readers [Very low quality evidence].
- The non-treponemal test using serum samples had a sensitivity of 64% (both readers) and specificities of 100% and 99% (reader 1 and 2 respectively) [Very low quality evidence].

SD Syphilis 3.0 assay (trep):

The study reported the diagnostic accuracy of the SD syphilis 3.0 assay comparing the treponemal line of the test to a treponemal reference standard (TPPA) for blood and serum samples.

- The SD syphilis 3.0 assay had a sensitivity of 51% and 54% (reader 1 and 2 respectively) and specificity of 100% (both readers) in blood samples in MSM [Low quality evidence].
- The SD syphilis 3.0 assay had a sensitivity of 80% and 83% (reader 1 and 2 respectively) and specificity of 100% (both readers) in serum samples in MSM [Low quality evidence].

Conclusions on the diagnostic accuracy of tests for syphilis in MSM

In Table 49, an overview is presented on the retrieved diagnostic accuracy tests in MSM.

Table 49 – Overview of the diagnostic accuracy to detect syphilis in MSM

MSM	Blood (in MSM)	Serum (in MSM)
Chembio DPP syp (non-trep + trep) Treponemal line	Sens: 65-69% Spec: 100% PPV: 95%	Sens: 58-64% Spec: 99-100% PPV: 94%
Chembio DPP syp (non-trep + trep) Non-treponemal line	Sens: 64% Spec: 100% PPV: 88-100%	Sens: 64% Spec: 99-100% PPV: 76-87%
SD syphilis 3.0 (trep)	Sens: 51-54% Spec: 100% PPV: 100%	Sens: 80-83% Spec: 100% PPV: 97-100%

In the GRADE profiles tabulated below (Table 50), an overview is presented of the number of studies per comparison, the quality assessment and the summary of findings. These considerations served as a basis for the formulation of the conclusions and the recommendations.

Table 50 – GRADE profiles: Diagnostic tests for syphilis in MSM, by sample type and assay

Study characteristics			Quality Assessment					Summary of findings Range % (95% CI)		
No. of studies	**Design**	**No.**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sensitivity (%)**	**Specificity (%)**	**Quality**
Chembio DPP syp (non-trep + trep) tests										
MSM – treponemal test with TPPA as reference standard using blood sample (prevalence 12.1%)										
1	Diagnostic cohort studies	227	Serious risk of bias[1]	Not applicable	No serious indirectness	Serious imprecision[3]	None	Reader 1: 65 (44 to 83) Reader 2: 69 (48 to 86)	Reader 1: 100 (97 to 100) Reader 2: 100 (97 to 100)	LOW
MSM – treponemal test with TPPA as reference standard using serum samples (prevalence 12.1%)										
1	Diagnostic cohort studies	205	Serious risk of bias[1]	Not applicable	No serious indirectness	Serious imprecision[3]	None	Reader 1: 58 (37 to 77) Reader 2: 64 (43 to 82)	Reader 1: 100 (97 to 100) Reader 2: 99 (97 to 100)	LOW
MSM – non-treponemal test with RPR as reference standard using blood samples (prevalence 5.5%)										
1	Diagnostic cohort studies	227	Serious risk of bias[1]	Not applicable	No serious indirectness	Very serious imprecision[3]	None	Reader 1: 64 (31 to 89) Reader 2: 64 (31 to 89)	Reader 1: 100 (98 to 100) Reader 2: 100 (97 to 100)	VERY LOW
MSM – non-treponemal test with RPR as reference standard using serum samples (prevalence 5.5%)										
1	Diagnostic cohort studies	205	Serious risk of bias[1]	Not applicable	No serious indirectness	Very serious imprecision[3]	None	Reader 1: 64 (31 to 89) Reader 2: 64 (31 to 89)	Reader 1: 100 (97 to 100) Reader 2: 99 (96 to 100)	VERY LOW
Point of care – treponemal test										

Study characteristics			Quality Assessment					Summary of findings Range % (95% CI)		Quality
No. of studies	**Design**	**No.**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sensitivity (%)**	**Specificity (%)**	
MSM – SD Syphilis 3.0 assay using blood sample (prevalence 12.1%)										
1	Diagnostic cohort studies	289	Serious risk of bias[1]	Not applicable	No serious indirectness	Serious imprecision[3]	None	Reader 1: 51 (34 to 69) Reader 2: 54 (37 to 71)	Reader 1: 100 (99 to 100) Reader 2: 100 (99 to 100)	LOW
MSM – SD Syphilis 3.0 assay using serum sample (prevalence 12.1%)										
1	Diagnostic cohort studies	227	Serious risk of bias[1]	Not applicable	No serious indirectness	Serious imprecision[3]	None	Reader 1: 80 (63 to 92) Reader 2: 83 (66 to 93)	Reader 1: 100 (99 to 100) Reader 2: 100 (98 to 100)	LOW

[1] Risk of bias was assessed using the QUADAS-2 checklist. If there was one criterion with a high risk of bias the study was considered to have a serious risk of bias. If there were two or more criteria with a high risk of bias the study was considered to have a very serious risk of bias. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias. The evidence was downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

[3] Imprecision was based on the range of point estimates or, if only one study contributed to the evidence, the 95% CI around the single study. As a general rule a variation of 0–20% was considered precise, 20–40% serious imprecision, and >40% very serious imprecision. Imprecision was assessed on the primary outcome measure for decision-making.

3.13.3.4 Clinical outcomes of tests for syphilis

User friendly aspects of the tests for syphilis

Women and men:

EIA IgM/IgG test

One study[66] reported the time required to perform the EIA IgM/IgG test in 80 specimens.
The EIA IgM/IgG test took 120 minutes, but with incubation times (microbiologist free time) of both 60 and 30 minutes.
The VDRL reference standard took 150 minutes approximately (to resolve both reactive and non-reactive specimens).

EIA IgM/IgG specimens are pipetted only once into the assay plate wells, while for the VDRL, specimens found to be reactive must be diluted (3-5 dilutions per specimen, each requiring multiple pipetting steps) and subsequently reanalysed.

Chembio DPP HIV-syp (trep)

Another study[62] reported that the Chembio DPP HIV-syp (trep) test requires a pre-dilution step, use of second buffer and multiple steps, which may add some level of complexity for providers with limited laboratory expertise. The presence of three lines (one for control, a second for syphilis and a third for HIV) may cause misinterpretation of results by less trained professionals.

Harmful effects

The outcomes on harms, such as pain and discomfort, were not reported for women, MSM and men.

3.13.3.5 Conclusions: Diagnostic accuracy of tests for syphilis

Direct detection methods

- One study assessed the performance of the TpPCR on swabs and biopsies from ulcers from a population of whom many patients were MSM, HIV patients, and other patients with high rates of STI; in this sample the TpPCR had a low sensitivity of 80% but a high specificity of 98%. The PCR may be useful for diagnosis in patients with lesions that are suspicious of syphilis. Although swabs could possibly be taken in first line settings, biopsies will need specialist attention.

Serological tests

- Two studies compared EIA IgG and EIA IgM/IgG testing on serum samples from men and women:
  - The EIA IgG reported a low sensitivity of 85% while the EIA IgM/IgG had a considerably higher sensitivity of 98% in serum samples. The relatively poor sensitivity of EIA IgG may be due to the small number of syphilis-positive cases included in this study but more importantly, only the IgG class of specific antibodies is detected so that early syphilis cases may have been missed.
  - While the EIA IgM/IgG was less sensitive than the VDRL, it was far more specific than the VDRL. Moreover, the EIA IgM/IgG was able to test samples more quickly than VDRL and could be considered more user friendly.
- The serum samples had higher sensitivities compared to the blood samples in all reported studies.
- No conclusion can be drawn on harms as there was no evidence for this outcome.

POC tests

- Chembio DPP syp (non-trep + trep) test had higher sensitivities (89-97%) in the serum samples, from a mixed population of men and women, for the treponemal line and the non-treponemal component of the dual test compared to the blood samples (48-53%) while specificities were consistently high ranging from 95-99% in both serum and blood. The combined result of treponemal and non-treponemal result had a sensitivity of 90% and specificity of 100%. This dual test (non-trep + trep) would be useful for the serological diagnosis of syphilis for hard-to-reach populations or/and health care settings where patients may fail to return for their laboratory results.
- The dual HIV-syphilis tests (Chembio DPP HIV-syp (trep) and SD HIV-syp (trep)) on blood samples (mixed population) had low sensitivities of 46-47% with high specificities of 99-100%. However, the tests performed better on serum samples with sensitivity of 99% for Chembio test and 70% for the SD test and specificities of 99-100%.
- The triple HIV-HCV-syphilis Chembio test had a low sensitivity of 44% for syphilis while specificity remained high at 99%. For HIV and HCV, sensitivity and specificity were very high (100% and 99.9% for HIV; 91.8% and 99.3% for HCV) using blood samples (mixed population). The good sensitivity of the HIV and HCV on the HIV-HCV-Syphilis rapid test suggests that combining the tests onto one device is possible. However, the treponemal test in this case does not perform well. In addition, these tests only detect the treponemal antibody and the distinction between an active case and a treated case of syphilis is difficult. When combining the tests onto one device it may be advantageous to include both the treponemal and nontreponemal tests to avoid over diagnosis and treatment.
- The Chembio DPP syp (non-trep + trep) test had similar low sensitivities ranging from 58-69% using both serum and blood samples from MSM. The treponemal line of the test with blood samples had higher sensitivities ranging from 65-69% compared to the serum samples 58-64%. The non-treponemal test reported a sensitivity of 64% in both serum and blood samples. There were high specificities ranging from 99-100% for all tests and sample types.
- The SD syphilis 3.0 assay (trep) (MSM population) had a higher sensitivity of 80-83% in serum samples compared to 51-54% in blood samples, while both had a specificity of 100%.
- No conclusion can be drawn on user friendly aspects of the test as there was no evidence on this outcome.

Testing strategies – algorithm

- The reverse algorithm may identify additional positive results that would be missed with the traditional algorithm. Early infections are more likely to be false negative when a non-treponemal test is first performed as sensitivity is low for early infections.
- The reverse algorithm may lead to a higher number of false positive results during diagnosis. Currently, the non-treponemal tests are performed by automisation and are less labour intensive. A second non-treponemal test will reduce the false positive rate in the updated reverse algorithm.
- There is not enough evidence in the retrieved studies to recommend one type of algorithm over the other.

3.13.3.6 Conclusions: Clinical outcomes of tests for syphilis

- No conclusion can be drawn for the preferred method of sample selection from a patient point of view as there was no evidence for this outcome.
- No conclusion can be drawn on harms as there was no evidence for this outcome.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	• Algorithms with a treponemal assay line that do NOT add a non-treponemal assay line into the testing scheme will have a high false positive rate. Old infections will be detected as well. This results in overtreatment of patients who may have evidence of an old infection but no recent or active syphilis infection. Adding a second treponemal test increases specificity and reduces the false positive results encountered on the automated analysers. Although confirmation of a positive treponemal test and ruling out a false positive test may be important for counselling, notification and have a psychological impact, it has limited impact on treatment. • POC tests have low sensitivities and will result in false negatives. They may be an option for hard to reach groups who will not test or cannot access testing but ideally in all situations a blood sample should be taken and tested at the laboratory. • Because of the seriousness and chronic aspect of the infection, each positive test should be investigated further or treated. • There is no evidence on the harms of the use of the diagnostic tests from the additional search.
Quality of evidence	Update literature search: 7 observational studies with very low to low quality evidence. One observational study evaluating the reverse versus traditional algorithm obtained a moderate level of evidence.
Costs (resource allocation)	• While both nontreponemal tests and treponemal tests are relatively inexpensive, both require specialized equipment, technical expertise, and a significant time commitment to accurately perform; these factors can limit the ability of many facilities to provide in-house testing services, leading to the higher per test costs and treatment delays associated with off-site testing. • Many facilities in Belgium have reversed their testing procedure for syphilis by using automated, high-throughput treponemal enzyme-linked immunoassays (EIAs) for screening to curtail personnel expenses through specimen batch testing. The procedure can reduce the rate of false positive RPR results; however, in high prevalence settings, such as urban-based STI clinics, it might result in overtesting due to a higher proportion of false positives from previously treated infections. It also creates the need for either a secondary treponemal test or clinical assessment based on a patient's sexual and treatment history to confirm positive results, which merely shifts costs from one operational setting to another within the same diagnostic chain.

	• For pregnant women: the prevalence of syphilis is low in Belgium but a universal screening is supported by the fact that an effective treatment is available, screening is cheap and a selective approach based on risk factors is inaccurate. • The cost of each test is low and the co-payment rules are stipulated (reimbursement by INAMI/RIZIV and out-of-pocket payments). When a patient is hospitalized (general hospital), he does not pay for the syphilis tests themselves but is charged 7.44€ per hospital stay to cover any biological test performed during his hospital stay, whatever their purposes. Besides this, the hospital further receives 25% of the full cost of each test performed, and a per diem per inpatient day, inclusive the first day (the amount of this per diem depends on the case-mix of each hospital (APR-DRG)). • POC tests offer many advantages: a rapid, accurate, and easy-to-use dual-component test with a low cost providing simultaneous screening for syphilis and HIV from a single finger stick; results are rapidly obtained (within 15-20 minutes). However, the performance of the POC tests can be influenced by human factors such as the ability to properly follow the rapid testing procedures (capillary blood taking, correct timing of adding the buffer and reading)[67]
Patients values and preferences	Patient's values and preferences were not investigated in the studies retained for the guidelines. Diagnostic procedures for minors: If the professional considers that the child is mature enough to give his or her consent, his/her informed consent is sufficient (art. 12 § 2 of the Patient Rights Act). The professional is not only guided by the age and maturity of the child, but also by the nature and consequences of the intervention or treatment. As the severity of the procedure and the associated risks increase, the maturity requirements will also be higher. .[100] Competent minors can independently decide on low-risk medical interventions. These may include tests or treatments with few side effects (e.g., taking blood samples, prescribing contraceptives, etc.) or interventions that pose few health risks (e.g. tooth extraction, etc.). Conducting an STI diagnostic test is a low-risk procedure. It is important to note that this is the ability to accept a diagnostic test. This should be distinguished from the ability to authorize acts that affect sexual integrity. Just because you were not legally capable of consenting to sexual intercourse does not mean that you could not legally consent to a (medical) act (to be) related to sexual intercourse (theoretically punishable).

Table 51 – Cost of diagnostic tests for syphilis

	Nomenclature code (INAMI-RIZIV)	Test	Reimbursement interval if applicable	Full Cost in euros*	Reimbursement in euros*	Out-of-pocket in euros*
Syphilis	552716-552720	serum, plasma or cerebrospinal fluid non-specific Ag (RPR or VDRL)		2.50	0.63	0.0
	552731-552742	serum, plasma or cerebro-spinal fluid specific Ag		7.81	1.95	0.0

*Note. * no difference between ambulatory/hospitalisation, nor between patients with/without preferential reimbursement; a Maximum number ONCE for one clinical session*

3.13.4 Recommendations: Who to test for syphilis

Who to test for syphilis	Strength of Recommendations	Level of Evidence
All pregnant women in the first trimester or at the first antenatal visit. For pregnant women with high risk sexual behaviour or at increased risk for syphilis as identified below, repeat test in the third trimester whatever the result of the first test.	Strong	Moderate
Patients with symptoms suspicious of syphilis (see best practices for overview symptoms).	Weak	Very low
For asymptomatic patients with high risk sexual behaviour or at increased risk for syphilis: 1. Sex worker of any gender 2. MSM with high risk behaviour • unprotected sexual contacts (including deep kissing) in non-exclusively monogamous relationships • who are on PrEP • with a recent HIV diagnosis • with a syphilis diagnosis in the past 3. Patient or sex partner originates or travels to and from a country where the prevalence of syphilis is known to be high. See WHO map (https://www.who.int/gho/sti/en/). Countries with a prevalence above 1% include: • Sub-Saharan Africa: Mauritania, Mali, Senegal, Guinea, Liberia, Côte d'Ivoire, Ghana, Togo, Gabon, Chad, Sudan, Eritrea, Ethiopia, Central African Republic, South Sudan, Somalia, Kenya, Gabon, Democratic Republic of Congo, Rwanda, Uganda, United Republic of Tanzania, Zambia, Mozambique, Namibia, Botswana, South Africa, Madagascar, Zimbabwe • North African countries: Morocco, Algeria • Indonesia and Papua New Guinea • South and middle America: Venezuela, Colombia, Dominican Republic, Argentina, Paraguay • Romania, Mongolia 4. Heterosexual patient with unprotected oral, anal or vaginal intercourse in non-exclusively monogamous relationships with/whenever • concurrent partners • multiple partners over a short time period • partner as defined above in 1, 2, or 3 • an STI diagnosis including HIV in the past year • partners in anonymous setting	Weak	Very low

5. Adolescents and young people up to the age of 29 years with unprotected oral, anal or vaginal intercourse in monogamous relationships with/whenever • a chlamydia, gonorrhoea, or HIV is diagnosed • partner as defined above in categories 1, 2, 3 or 4 Test for syphilis whenever: • a newborn/baby or other whenever the other was diagnosed with syphilis • in case of abortion • sexual partner with suspected or confirmed syphilis • all patients who are newly diagnosed with an STI including HIV • patients with a newly diagnosed hepatitis B or hepatitis C that may have been acquired through sexual transmission	Weak	Very low

3.13.5 Recommendations: Which sample to take for syphilis diagnosis

Which sample to take for syphilis diagnosis	Strength of Recommendations	Level of Evidence
The cornerstone of diagnosis are serological tests: Sample venous blood for serologic tests.	Strong	High
In case of a chancre, i.e. a single painless, indurated, clean base, clear serum, no blistering ± regional lymphadenopathy, depending on the local laboratory procedures: Sample any suspicious anogenital or oral ulcer by swab for PCR.	Weak	High

3.13.6 Recommendation: Which tests for syphilis diagnosis

Which tests to use for syphilis diagnosis	Strength of Recommendation	Level of Evidence
On the basis of the current evidence we do not recommend to offer POC testing for the diagnosis of syphilis in first line.	Strong	Low

3.13.7 Choice of tests for syphilis diagnosis: Good practice statements

Choice of tests for syphilis diagnosis: Good practice statements
Because final diagnosis is made on grounds of clinical picture AND laboratory results: • Communicate with laboratory all relevant information from the patient's history and clinical diagnosis regarding symptoms, stage of infection, and previous infection, HIV status, pregnancy, and risk behaviours
Investigate ANY positive result: • After having sent samples to a laboratory, results could take 3 to 7 days. Make sure that the testing algorithm chosen by the laboratory is followed through (all diagnostic tests, including trep tests and non-trep tests are performed). If this is not clear, then discuss with laboratory.   • If the results are difficult to interpret ask a colleague knowledgeable in syphilis for clarifications and / or refer.

3.14 Treatment of syphilis: Information and advice for the patient

3.14.1 Recommendations from international guidelines

Table 52 – Recommendations from international guidelines – Information for the patient

Source	Recommendation for 1st line	Remarks	Alternatives
INFORMATION, EXPLANATION AND ADVICE FOR THE PATIENT			
BASHH 2015[6]	All patients with syphilis should have screening for other STIs including HIV: 1A Patients should be given a clear explanation of their diagnosis of syphilis and its implications, reinforced with written information: 1D Patients with early, infectious syphilis should be advised to abstain from sex until any lesions (if any) have resolved or until two weeks after treatment completion: 1C		
IUSTI 2014[11]	Clear information, ideally written such as the IUSTI leaflet, should be given to all individuals with syphilis and their sexual contacts. Sexual contacts should include all those individuals who have had oral, vaginal or anal intercourse with infected individuals, whether or not barrier protection was used.		

3.14.2 Recommendations regarding syphilis information and advice for the patient

Syphilis information and advice for the patient	Strength of Recommendations	Level of Evidence
Patients with early, infectious syphilis should be advised to abstain from sex until one week after start of treatment.	Weak	Very low
Patients (and their sex partners) should be given information about their infection, including details about transmission, prevention and complications. Verbal information needs to be reinforced with written support or video material such as, hyperlinks towards scientific websites or organisations dedicated to STIs leaflets, brochures.	Weak	Very low
All patients with a syphilis diagnosis should be offered testing for other STI including HIV.	Weak	Very low

3.15 Treatment of syphilis: initiation of therapy and referral to second line

3.15.1 Recommendation regarding initiation of syphilis therapy

Initiation of syphilis therapy	Strength of Recommendation	Level of Evidence
Treatment is to be started for the following reasons: • Active syphilis • Positive serological tests in combination with clinical information • On epidemiological grounds: Immediate epidemiological treatment for sexual contacts should be considered, especially of pregnant partners	Weak	Very low

3.15.2 Recognising syphilis clinical symptoms: Good practice statements

Recognising syphilis clinical symptoms: Good practice statements

Patients with symptoms that are suspicious for syphilis

- Any chancre-like anogenital ulcer should be considered syphilis unless proven otherwise
- Primary syphilitic anogenital or oral ulcer / chancre
  - regional lymphadenopathy
  - single painless, indurated, clean base, clear serum, no blistering
  - atypical, multiple, painful, deep, indistinguishable from herpes
- Symptomatic secondary syphilis
  - non-itching skin rash (roseola, papular syphilids)
  - mucocutaneous lesions – condylomata lata
  - fever, generalized lymphadenopathy, hepatitis, splenomegaly, periostitis, arthritis and glomerulonephritis
  - meningitis, cranial nerve palsies
  - auricular and ophthalmic abnormalities (such as uveitis, retinitis, otitis and papilloedema)
- Symptomatic tertiary syphilis
  - gummatous syphilis: nodules/plaques or ulcers (skin, mucosae, visceral)
  - early or late neurosyphilis: stroke, myelitis, meningitis, cranial nerve dysfunction, general paresis, tabes dorsalis, unexplained sudden visual loss, unexplained sudden deafness
  - cardiovascular syphilis: aortic regurgitation, stenosis of coronary ostia, aortic aneurysm (mainly thoracic)

3.15.3 When to refer the patient to the second line for syphilis: Good practice statements

When to refer to the second line for syphilis: Good practice statements

Patients should be referred to the second line[μ] before initiation of treatment:

- pregnancy (also refer to gynaecologist)
- clinical features of symptomatic late syphilis[£]
- neurological symptoms or suspicion of neurosyphilis
- suspicion of ocular syphilis
- cardiovascular symptoms
- complications

Guided by results serology after initiation of treatment

- difficult interpretation of serologic tests that may affect treatment duration
- repeat infections

Note. [μ] Referral to the appropriate specialist or medical colleague knowledgeable in syphilis is guided by the symptoms and their severity, or other characteristics such as pregnancy [£]gummatous disease, cardiovascular disease, ocular disease, neurological disease

3.16 Treatment of syphilis: Treatment choice in men and women

3.16.1 Recommendations from international guidelines

Source and target population	Recommendation for 1st line	Remarks	Alternatives
TREATMENT OF EARLY SYPHILIS (PRIMARY, SECONDARY AND EARLY LATENT SYPHILIS; ACQUIRED ≤ 1 YEAR PREVIOUSLY)			
IUSTI 2014[11]	***First line therapy option*** Benzathine penicillin G (BPG) 2.4 million units intramuscularly (IM) (one injection of 2.4 million units or 1.2 million units in each buttock) on day 1 [Ib; A] ***Second line therapy option*** Procaine penicillin 600 000 units IM daily for 10–14 days, i.e. if BPG is not available [IIb; B]	Replacing part (i.e. 0.5–1 cc) of the solvent by lidocaine 1% solution without epinephrine may reduce the discomfort associated with injection. This is not feasible in case of premounted BPG syringes. Patients should be kept for 30 min clinical review after injection.	***Penicillin allergy or parenteral treatment refused:*** 1. Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally for 14 days [III; B]; 2. Azithromycin 2 g orally single dose [I; B] ***Bleeding disorders:*** 1. Ceftriaxone 500 mg–1 g subcutaneously or IV daily for 10 days [III; B] 2. Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally for 14 days [III; B] 3. Azithromycin 2 g oral single dose [I; B]
IUSTI 2014[11] HIV patients	Treatment should be given as for non-HIV infected patients, although there are very few data on the use of second line options.		
IUSTI 2014[11] Sexual partners	Immediate epidemiological treatment for sexual contacts should be considered (especially of pregnant partners) unless contacts are able to attend regularly for exclusion of syphilis through clinical and serological examination (0, 4 weeks and 3 months).		
BASHH 2015[6]	Parenteral treatment with the appropriate penicillin preparation is the treatment of choice: 1B.		Macrolide antibiotics are to be used if only available option and when follow-up can be assured: 1B.

BASHH 2015[6]	***Potentially incubating syphilis/ epidemiological treatment***: 1. Benzathine penicillin 2.4 MU IM single dose: 1C 2. Doxycycline 100 mg PO twice daily 14 days: 1C 3. Azithromycin 2 g PO stat: 2C ***Early syphilis (primary, secondary and early latent)***: Benzathine penicillin G 2.4 MU IM single dose: 1B	Resistance limits the use of macrolide antibiotics and they should be used as a last resort only when follow-up can be assured.	***Potentially incubating syphilis/ epidemiological treatment***: No alternative ***Early syphilis (primary, secondary and early latent)***: 1. Procaine penicillin G 600 000 units IM daily x 10 days: 1C 2. Doxycycline 100 mg PO twice daily x 14 days: 1C 3. Ceftriaxone 500 mg IM daily x 10 days: 1C 4. Amoxycillin 500 mg PO four times daily plus Probenecid 500 mg x 14 days: 1C 5. Azithromycin 2 g PO stat or Azithromycin 500 mg daily x 10 days: 2B 6. Erythromycin 500 mg PO four times daily x 14 days: 2B
WHO 2016[27] All adults and adolescents (10–19 years of age), including people living with HIV, people who are immunocompromised and key populations, including sex workers, MSM and transgender persons.	In adults and adolescents with early syphilis, WHO recommends benzathine penicillin G 2.4 million units once intramuscularly over no treatment (Strong recommendation, very low quality evidence). In adults and adolescents with early syphilis, WHO suggests using benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin G 1.2 million units 10–14 days intramuscularly (Conditional recommendation, very low quality evidence).	Doxycycline is preferred over ceftriaxone due to its lower cost and oral administration. Azithromycin is an option in special circumstances only when local susceptibility to azithromycin is likely. If the stage of syphilis is unknown, follow recommendations for people with late syphilis.	When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy) or are not available (e.g. due to stock-outs), the WHO STI guideline suggests using doxycycline 100 mg twice daily orally for 14 days or ceftriaxone 1 g intramuscularly once daily for 10–14 days, or, in special circumstances, azithromycin 2 g once orally.
CDC 2015[10]	***Recommended Regimen for Adults***: Benzathine penicillin G 2.4 million units IM in a single dose	Parenteral penicillin G has been used effectively to achieve clinical resolution (i.e., the healing of lesions and prevention of sexual transmission) and to prevent late sequelae. However, no	Doxycycline to treat early and late latent syphilis is an acceptable alternate option if penicillin cannot be used. Azithromycin as a single 2-g oral dose has been effective for

		comparative trials have been conducted to guide the selection of an optimal penicillin regimen. T. pallidum chromosomal mutations associated with azithromycin (and other macrolide) resistance and treatment failures have been documented in multiple geographical areas in the United States. Accordingly, azithromycin should be used with caution only when treatment with penicillin or doxycycline is not feasible.	treating early syphilis in some settings. Azithromycin should not be used in MSM or pregnant women. Careful follow-up of patients receiving any alternative therapies is essential.
CDC 2015[10] HIV patients	CDC does not recommend the use of enhanced antimicrobial therapy for early syphilis with additional doses of BPG when treating HIV-infected persons with syphilis. CDC recommends to treat all patients with syphilis using similar therapeutic regimens irrespective of their HIV status.		
BASHH 2015[6] HIV patients	Testing and treatment for syphilis is the same HIV-positive individuals as those who are HIV negative.		
TREATMENT OF LATE SYPHILIS (I.E. ACQUIRED >1 YEAR PREVIOUSLY OR OF UNKNOWN DURATION)			
IUSTI 2014[11]	***First line therapy option*** Benzathine penicillin G (BPG) 2.4 million units IM (one injection 2.4 million units single dose or 1.2 million units in each buttock) weekly on day 1, 8 and 15 [III; B] ***Second line therapy option*** Procaine penicillin 600 000 units IM daily during 17–21 days, i.e. if BPG is not available [III; B]	Replacing part (i.e. 0.5–1 cc) of the solvent by lidocaine 1% solution without epinephrine may reduce the discomfort associated with injection. This is not possible in case of premounted syringes. Patients should be kept for 30 min clinical surveillance after injection.	***Penicillin allergy or parenteral treatment refused*** 1. Desensitization to penicillin 2. Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally during 21–28 days [III; B]
IUSTI 2014[11] HIV patients	Treatment should be given as for non-HIV infected patients, although there are very few data on the use of second line options.		
WHO 2016[27] All adults and adolescents (10–19 years of age), including people living	In adults and adolescents with late syphilis or unknown stage of syphilis, WHO recommends benzathine penicillin G 2.4		When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin

with HIV, people who are immunocompromised and key populations, including sex workers, MSM and transgender persons.	million units intramuscularly once weekly for three consecutive weeks over no treatment (Strong recommendation, very low quality evidence). In adults and adolescents with late syphilis or unknown stage of syphilis, WHO suggests benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units once daily for 20 days (Conditional recommendation, very low quality evidence). The interval between consecutive doses of benzathine penicillin should not exceed 14 days.		desensitization is not possible) or are not available (e.g. due to stock-outs), WHO suggests using doxycycline 100 mg twice daily orally for 30 days.
BASHH 2015[6]	Benzathine penicillin 2.4 MU IM weekly for three weeks (three doses): 1C. If drug administration is interrupted for more than one day at any point during the treatment course, it is recommended that the entire course is restarted.		1. Procaine penicillin 600,000 units IM once daily for 14 days 2. Doxycycline 100 mg PO twice daily for 28 days: 2D 3. Amoxycillin 2 g PO three times daily plus probenecid 500 mg four times daily for 28 days: 2C
REACTIONS TO TREATMENT			
BASHH 2015[6]	Advise patients of possible or common reactions to treatment and after administering parenteral therapy, observe for immediate reactions to treatment: 1C. Consider skin testing and subsequent penicillin desensitisation and treatment for those reporting allergy: 2A.	Patients should be warned of possible reactions to treatment. Facilities for resuscitation should be available in the treatment area. All patients should be kept on clinic premises for 15 minutes after receiving their first injection to observe for immediate adverse reactions. In addition, patients should be advised to seek urgent medical attention if they experience symptoms or signs of an allergic reaction: shortness of breath, itchy wheals on their skin, facial swelling or tightness in their chest or throat.	
IUSTI 2014[11]	Patients should be warned of possible reactions to treatment. Facilities for resuscitation should be available in the treatment area.	***Jarisch–Herxheimer reaction*** • An acute febrile illness with headache, myalgia, chills and rigors, resolving within 24 h.	

- Prevention of Jarisch–Herxheimer reaction: Prednisolone 20–60 mg daily for 3 days, starting antitreponemal treatment after 24 h of commencing prednisolone [IV; C] and antipyretics.

Procaine reaction (procaine psychosis, procaine mania, Hoigné syndrome)

- Due to inadvertent IV injection of procaine penicillin and may be minimized by the 'aspiration technique' of injection.
- Characterized by fear of impending death, may cause hallucinations or fits immediately after injection. Lasts less than 20 min.
- Management:
  - Exclude anaphylaxis
  - Calm and verbal reassurance; restraint may be necessary.
  - Diazepam 5–10 mg rectally/IV/IM if convulsions

Anaphylactic shock

- Facilities for treatment of anaphylaxis should be available as penicillin is one of the most frequent causes.
- Management:
  - Epinephrine (adrenaline) 1 : 1000 IM 0.5 mL followed by:
    - IM/IV antihistamine, e.g. chlorpheniramine 10 mg
    - IM/IV hydrocortisone 100 mg

3.16.2 Recommendations from national guides

Table 53 – Recommendations from national guides – Molecules and dosages for adults and adolescents

	First line				Allergy	Pregnant
Guide	**Indication**	**First choice**	**Second choice**	**Alternatives**	**First choice**	**First choice**
BAPCOC 2012 eerste lijn	Primary, secondary, latent (<1year)	Benzathine penicillin G 2.4 mU IM once	When penicillin contra indicated: Doxycycline 100 mg twice a day for 14 days NOT azithromycin	No information	Consider desensitization Doxycycline 100 mg twice a day 14 days	No doxycycline No information
	Latent >1year or unknown time of infection	Benzathine benzylpenicilline 2,4 milj IE IM on day 1,8 and 15	No information	No information	Consider desensitization Doxycycline 100 mg twice a day 28 days Ceftriaxone 1 gr IM or IV for 10 days (! Cross-allergy)	No information
BAPCOC ziekenhuis 2017*	Initial treatment	Benzathine penicillin G 2.4 mU IM once	When penicillin contra indicated: Ceftriaxone 1g IV or IM for 10 days	When penicillin contra indicated: Doxycycline 200 mg PO or 100 mg twice a day for 14 days	No information	No information
	Re-treatment (not neurosyphilis)	Benzathine penicillin G 2.4 mU IM thrice with one week interval	No information	No information	No information	No information
BVIKM[µ]		Benzathine penicillin G 2.4 mU IM once	Ceftriaxone 1g IV or IM for 10 days	Doxycycline 200 mg PO or 100 mg twice a day for 14 days	Ceftriaxone 1g IV or IM for 10 days OR Doxycycline 200 mg PO or 100 mg twice a day for 14 days	
Agentschap zorg en gezondheid 2017 (follows BAPCOC)	Primary, secundary, latent (<1year)	Benzathine penicilline 2,4 milj IE, IM (op 2 verschillende plaatsen), once	NOT azithromycin	No information	Consider desensitization Doxycycline 100 mg twice a day 14 days Ceftriaxone 1 gr IM or IV for 10 days (! Cross-allergy)	No doxycycline No information
	Latent >1year	Benzathine benzylpenicilline 2,4 milj IE IM on day 1,8 and 15	No information	No information	Consider desensitization Doxycycline 100 mg twice a day 28 days	No information

					Ceftriaxone 1 gr IM or IV for 10 days (! Cross-allergy)	
	Late syphilis or unknown time of infection	Benzathine benzylpenicilline 2,4 milj IE IM on day 1,8 and 15	No information	No information	No information	No information
Domus Medica 2017	Early syphilis and early latent	Benzathine benzylpenicilline 2,4 milj IE IM on day 1	No information	No information	No information	Benzathine benzylpenicilline 2,4 milj IE IM on day 1,8 and 15
	Late syphilis or unknown time of infection	Benzathine benzylpenicilline 2,4 milj IE IM on day 1,8 and 15	No information	No information	No information	No information
Ghapro 2014	Early syphilis and early latent	Benzathine benzylpenicilline 2,4 milj IE IM on day 1	No information	No information	No information	Benzathine benzylpenicilline 2,4 milj IE IM on day 1,8 and 15
	Late syphilis or unknown time of infection	Benzathine benzylpenicilline 2,4 milj IE IM on day 1,8 and 15	No information	No information	No information	No information

*Note. * Benzathine penicilline G: 0,5 to 1 cc of the solution liquid can be replaced by 1% lidocaïne without epinephrine to reduce the pain of the IM injection. Allergy for type 1 beta-lactam allergy, defined as anaphylactic shock and angioedema; not for pharyngeal infection. [µ] BVIKM: Belgische vereniging voor infectiologie en klinische microbiologie – SBIMC: Société belge d'infectiologie et de microbiologie clinique*

3.16.3 *Additional literature search: Treatment of uncomplicated syphilis in women and men including young people*

Globally, 18 studies reported treatment comparisons for syphilis in mixed populations of men and women.

2 RCTs[75, 76] and 5 observational studies[80, 82, 84, 86, 87] included patients with both HIV and syphilis; although they were mixed populations they were predominately male. One RCT[76] reported a 95% male population and the other RCT[75] reported 81% in the penicillin group and 93% in ceftriaxone group. The observational studies were also predominately male and reported 94% and above MSM populations apart from one study[80] that had a lower reported MSM of 47% and 40% in each arm.

Table 54 – Included primary studies

Reference	Treatment	Interventions	Definition Serological response	3 mo	6 mo	9 mo	12 mo	18 or 32 mo
Andrade 2017[76]	Single vs single	Benzathine Penicillin G 2.4 million units IM injection three times over 3 weeks ***versus*** Benzathine Penicillin G 2.4 million units IM injection once	Serological response defined as treatment success: a 4-fold decrease in initial RPR titer within 12 months follow-up.				x	
Cao 2017[77]	Single vs single	Benzathine Penicillin G 2.4 million units IM injection, once weekly for two weeks ***versus*** Ceftriaxone 1.0g intravenously, once daily for 10 days	Serological response defined as a ≥ 4-fold decline in the RPR titer.	x	x	x	x	
Costa-silva 2016[80]	Single vs single	Benzathine Penicillin G ***versus*** three weekly doses of Benzathine Penicillin G (dose not reported)	Serological response defined as a ≥4-fold decline in Venereal Disease Research Laboratory (VDRL) titer within 12 months.	x	x		x	
Drago 2016[78]	Triple vs single	Benzathine Penicillin G 2.4 million units by IM injection (one dose for people with primary, secondary and early latent syphilis, but 3 doses over 3 weeks for people with late latent syphilis) PLUS Ceftriaxone 1g by IM injection daily for 10 days followed by oral doxycycline 100mg twice daily for 20 days ***versus*** Benzathine Penicillin G 2.4 million units injection (one dose for people with primary, secondary and early latent syphilis, but 3 doses over 3 weeks for people with late latent syphilis)	Serological response defined as a 3 to 4-fold decrease in initial VDRL titer within 6 months of therapy.	x	x		x	
Ghanem 2006[81]	Single vs single	Benzathine Penicillin G 2.4 million units IM as single dose ***versus*** doxycycline100 mg orally, twice daily for 14 days	Serological response defined as failure with a 4-fold rise in RPR titers 30-400 days after treatment or the lack of a 4-fold drop in RPR titers 270-400 days after treatment with no evidence of reinfection on the basis of disease intervention specialists' records.				x (up to 400 days)	
Hook 2002[71]	Single vs single vs single	Azithromycin 2g single oral dose ***versus*** Azithromycin 4g, given by 2x2g doses (7 days apart) ***versus*** Penicillin G Benzathine 2.4 million units IM injection in one site or 4.8 million units (two IM injections of 2.4 million units given 7 days	Serological response defined as ≥ 2-dilution decrease in RPR titer.	x	x	x	x	

		apart) in the other site where this was standard practice at the time of the study						
Hook 2010[70]	Single vs single	Azithromycin 2g single oral dose ***versus*** Benzathine Penicillin G 2.4 million units IM (2 injections of 1.2 million units)	Serological response defined as a decrease in RPR titer at the time of the 6 month follow-up visit of ≥ 2-dilutions (4-fold) when compared with the initial RPR titer.	**x**	**x**			
Liu 2017[89]	Single vs single	Ceftriaxone, intravenous infusion of 1.0 g once daily for ten days ***versus*** Penicillin G procaine as IM injection of 800,000 units once daily for 15 days	Serological response defined as comparison of negative conversion rate in Toluidine red unheated serum test (TRUST).				**x**	
Riedner 2005[72]	Single vs single	Azithromycin 2 g orally ***versus*** Penicillin G Benzathine 2.4 million units IM	Serological response defined as a decrease in the RPR titer by at least two dilutions before or at the nine-month follow-up examination, with the titer at the time of treatment used as the baseline. For primary and secondary syphilis, complete resolution or improvement of lesions within one or two weeks after treatment was also required.	**x**	**x**	**x**		
Rolfs 1997[74]	Triple vs single	Penicillin G Benzathine 2.4 million units by IM injection (plus 2g amoxicillin and 500mg probenecid) ***versus*** Penicillin G Benzathine 2.4 million units by IM injection (plus placebo)	Treatment failure: when the RPR titer did not decrease by 2 or more dilutions or the test results did not become non-reactive after treatment.	**x**	**x**	**x**	**x**	
Salado 2016[82]	Single vs single	Doxycycline 100 mg orally twice daily for 14 days for early syphilis (primary, secondary and early latent stages) and for 30 days for late latent syphilis ***versus*** benzathine penicillin G, a single dose of IM 2.4 million units for early syphilis and 3 doses each at 1-week intervals for late latent syphilis.	Serological response rate defined as 4-fold or greater decline in RPR titers.	**x**	**x**	**x**	**x**	
Shao 2016[83]	Single vs single vs single	Minocycline 2 weeks, 100 mg orally, twice daily, for 14 days ***versus*** minocycline 4 weeks, 100 mg orally, twice daily, for 28 days ***versus*** benzathine penicillin G as a single IM dose of 2.4 million units	Serological response described as serological cure rate and defined as patients whose RPR titers became nonreactive after the disappearance of clinical manifestations of syphilis.				**x**	x **(2 years)**
Smith 2004[75]	Single vs dual	Ceftriaxone 1g IM injection daily for 15 days ***versus*** Procaine penicillin 2.4 million units by IM	Serological response defined as > 4-fold decline in RPR titer at median 32 months					**x**

		daily injection plus probenecid 500mg by mouth for 15 days	follow-up for penicillin group and 18 months follow-up for the ceftriaxone group.		
Tsai 2014[84]	Single vs single	Doxycycline as 100 mg twice daily for 14 days ***versus*** benzathine penicillin G as a single dose of 2.4 million units	Serological response defined as a decline of RPR titer by 4-fold or greater from baseline value.	**x**	**x**
Wong 2008[88]	Single vs single/single	Benzathine Penicillin G 2.4 million units in a single dose intramuscularly ***versus*** doxycycline 100 mg orally, twice daily for 14 days or tetracycline 500 mg orally, 4 times daily for 14 days.	Serological response defined as a minimum 4-fold decrease in baseline rapid plasma reagin test antibody titer within 6 months, or ≥8-fold decrease within 12 months, or ≥16-fold decrease by 24 months.	x **(minimum)**	
Xiao 2017[85]	Single vs single	Doxycycline 100 mg orally twice daily for 14 days ***versus*** benzathine penicillin G 2.4 million units IM single dose	Serological response defined as a decline of RPR titer by 4-fold or greater from the baseline value at 6 or 12 months of doxycycline or BPG treatment if initial RPR titer was 1:8 or higher. If RPR titer was 1:4, 1:2, or 1:1 at baseline for primary syphilis or secondary syphilis, successful treatment was considered to be when the lesions disappeared and RPR turned to be negative after treatment.		**x**
Yang 2014[86]	Single vs single	Penicillin G Benzathine single dose (2.4 million units, 1179 IU/mg) IM ***versus*** Penicillin G Benzathine triple dose (3 weekly doses of 2.4 million units, 1179 IU/mg) IM	Serological response rate defined as 4-fold or greater decline in RPR titers at 12th month follow-up visit when compared with baseline titers.		**x**
Yang 2016[87]	Triple vs single	Single-dose benzathine Penicillin G (2.4 million units) ***versus*** azithromycin 2g (route of administration was not reported)	Serological response rate Defined as a decline of an RPR titer by ≥4-fold from the baseline value at 12 months of azithromycin or BPG treatment.		**x**

3.16.3.1 Treatment of syphilis in men and women (mixed population)

TREATMENT COMPARISONS WITH PENICILLIN BASED TREATMENT

Azithromycin 2g (single orally) or 4g (orally twice a week apart) vs Penicillin G Benzathine (BPG) 2.4 million units IM once or twice 7 days apart

3 RCTs and 1 observational study compared azithromycin with BPG.

One small RCT study[71] with 3 arms comprising 74 participants evaluated BPG (2.4 million units IM in Birmingham or 2.4 million units IM twice 7 days apart in New Orleans), azithromycin 2g (orally single dose) and azithromycin 4g (orally 2 x 2g doses 6-8 days apart) in men and women. The population was patients with early (primary, secondary or early latent) syphilis and 4% were HIV positive. The study reported that 57% were male in BPG group, 62% in azithromycin 2g group and 50% were male in azithromycin 4g group.

Another RCT[72] comprising 328 participants evaluated syphilis treatment with azithromycin (2g orally) with BPG (2.4 million units intramuscularly) in men and women. The population was participants with early symptomatic syphilis (primary or secondary) or high-titer latent syphilis. 52% of the study population were HIV positive. This study[71] did not provide crude numbers and only reported percentages. However, the Cochrane review by Bai 2012[68] did report the crude figures which we have used in this report.

Another RCT[70] comprising 517 participants evaluated syphilis treatment with azithromycin (2 g orally) with BPG (2.4 million units intramuscularly) in men and women. The population was people with early syphilis (primary, secondary or early latent) and HIV negative.

The evidence suggested that there was no difference in serological response at 3, 6 (3 studies, low quality), 9 (2 studies, low quality) or 12 months (1 study, low quality). The evidence suggested that the BPG may provide a benefit in fewer cases of the following adverse events: gastrointestinal, nausea and diarrhoea (1 study, very low quality). However, the evidence suggested that there was no difference in vomiting and an increase in Jarisch-Herxheimer events in the BPG group (1 study, very low quality).

Clinical cure, compliance and antimicrobial resistance were not reported.

One observational study[87] comprising 399 participants, evaluated azithromycin (2g single dose) compared to BPG (2.4 million units, single dose) in men. The population was participants with HIV and early syphilis (primary, secondary or early latent) and over 99% were recorded as MSM. The evidence suggested that there was no difference in serological response at 12 months (1 study, very low quality).

Clinical cure, adverse events, compliance and antimicrobial resistance were not reported.

BPG 2.4 million units IM once + amoxicillin 2g + probenecid 500 mg vs BPG 2.4 million units IM once (plus placebo)

One RCT[74] comprising 541 participants evaluated syphilis treatment with combined therapy of BPG (2.4 million units IM once) plus amoxicillin (2 g) and probenecid (500 mg orally three times a day for 10 days) compared to standard therapy of BPG (2.4 million units IM once) in men and women. The population was patients with untreated primary, secondary or early latent syphilis and 19% were HIV positive. In the HIV positive population 84% were male while 68% were male in HIV negative population. The evidence suggested that there was no difference in treatment failure at 3, 6 (and adjusted[b]), 9 and 12 months (1 study, very low quality). However, the evidence suggested that there were more cases of diarrhoea in the combined therapy compared to BPG (1 study, low quality).

[b] The 6 month raw data was adjusted for age, sex, stage of syphilis, HIV status, initial RPR titre, and study site, compliance and incidental antibiotic use in a multivariate logistic regression.

The authors reported that the patients did not differ with regard to compliance with medication between the groups. Clinical cure and antimicrobial resistance were not reported.

BPG 2.4 million units IM (one dose for primary, secondary and early latent syphilis, but 3 doses over 3 weeks for late latent syphilis) + ceftriaxone 1g IM daily for 10 days and oral doxycycline 100mg twice daily for 20 days vs BPG 2.4 million units IM (one dose for primary, secondary and early latent syphilis, but 3 doses over 3 weeks for late latent syphilis)

One small RCT[78] comprising 69 participants evaluated syphilis treatment with BPG (2.4 million units IM once for primary, secondary and early latent but 3 injections over 3 consecutive weeks for late latent) plus ceftriaxone (1g/daily for 10 days by IM) followed by oral doxycycline (100mg/twice daily for 20 days) compared to BPG (2.4 million units IM once for primary, secondary and early latent but 3 injections over 3 consecutive weeks for late latent) in men and women. The population was patients with syphilis (primary, secondary, early latent or late latent) and 9% were HIV positive. The majority of patients were men with 74% in the BPG group and 77% in the BPG + ceftriaxone + doxycycline group. The evidence suggested that the combined therapy (BPG + ceftriaxone + doxycycline) may provide a benefit in an increased number with serological response at 3, 6 and 12 months compared to the BPG group (1 study, very low quality). However, the evidence suggested that there was no difference in adverse events between the groups (1 study, very low quality).

Clinical cure, compliance and antimicrobial resistance were not reported.

Ceftriaxone 1 g IV once daily for 10 days vs BPG 2.4 million units IM twice 7 days apart

One RCT[77] comprising of 230 participants evaluated syphilis treatment with ceftriaxone (1 g intravenously, once daily for 10 days) compared to BPG (2.4 million units IM, once weekly for two weeks) in men and women. The population was HIV negative men and women with early syphilis (primary, secondary or early latent). The evidence suggested that the ceftriaxone may provide a benefit in an increased number with serological response compared to BPG at 6, 9 and 12 months (1 study, very low quality). However, the evidence suggested no difference in serological response at 14 days (1 study, very low quality) or at 3 months (1 study, low quality), adverse events (serious adverse events or drug related, non-cure as serofast at 12 months (1 study, very low quality) or clinical cure defined as skin lesions disappeared within one month (1 study, low quality). The evidence suggested that there were more cases of probable Jarisch-Herxheimer in the ceftriaxone group compared to BPG group (1 study, very low quality). Compliance and antimicrobial resistance were not reported.

Ceftriaxone 1 g IV once daily for 10 days vs penicillin G procaine IM of 800,000 units once daily for 15 days

One small RCT[79] comprising of 60 participants evaluated syphilis treatment with ceftriaxone (1g once daily for ten days) compared to penicillin G procaine (800,000 units once daily for 15 days) in men and women. The population was participants with early stage syphilis and none had HIV. The evidence suggested that the penicillin G procaine may provide a benefit in increased number with clinical cure defined as subsidence of skin lesions after one week) (1 study, very low quality). However, the evidence suggested that there was no difference in serological response (1 study, low quality) or non-cure described as incidence of seroresistance (1 study, very low quality). Adverse events, compliance and antimicrobial resistance were not reported.

Minocycline 2 weeks (100 mg orally, twice daily for 14 days) or minocycline 4 weeks (100 mg orally, twice daily for 28 days) vs BPG 2.4 million units IM once

One observational study[83] with 3 arms comprising 196 participants evaluated minocycline 2 weeks (100mg orally, twice daily for 14 days) compared to minocycline 4 weeks (100mg orally, twice daily for 28 days) compared to BPG (2.4 million units IM) in men and women. The population was men and women without HIV with a first time diagnosis of early syphilis (primary, secondary or early latent stages).

When comparing the BPG arm with the minocycline arms combined, the evidence suggested there was no difference in serological response at 2 years (1 study, very low quality). Adverse events, clinical cure, compliance and antimicrobial resistance were not reported.

Doxycycline 100 mg orally twice daily for 14 days (except late latent syphilis which was given for 30 days) vs BPG 2.4 million units IM once (except late latent syphilis which was given as three doses one week apart)

Four observational studies[81, 82, 84, 85] comprising 1224 participants evaluated syphilis treatment with doxycycline (100 mg orally twice daily for 14 days) compared to BPG (2.4 million units IM as a single dose) in men and women. One study[82] gave BPG as 2.4 million units IM as a single dose for early syphilis and 3 doses each at 1-week intervals for late latent syphilis. At the beginning of this study period 15 patients were treated with procaine penicillin (1 dose of 600,000 units once daily for ten days) these cases were grouped with BPG treated cases. The population of 2 studies[82, 84] were HIV positive and predominately male with 95-96% reported MSM. The other two studies[81, 85] had a population of men and women with one study[85] having no HIV positive participants and the other[81] reported the proportion of HIV positive participants as 5.9% in the doxycycline group and 13.7% in the BPG group. The population in 3 studies[81, 84, 85] was early syphilis (primary, secondary or early latent) whilst the other study[82] included all participants diagnosed with syphilis that included primary, secondary, early latent, late latent, relapse stages of syphilis.

The evidence suggested that there was no difference in serological response at 3 months (1 study, very low quality), 9 months (1 study, very low quality) and 12 months (4 studies, very low quality). However, the evidence suggested that BPG may provide a benefit in increased number with serological response at 6 months (2 studies, very low quality). Adverse events, clinical cure, compliance and antimicrobial resistance were not reported

Doxycycline 100mg orally, twice daily for 14 days or tetracycline 500 mg orally, 4 times daily for 14 days vs BPG 2.4 million units IM once

One observational study[88] comprising 445 participants evaluated BPG (2.4 million units IM) compared to doxycycline (100 mg twice a day for 14 days) OR tetracycline (500 mg 4 times a day for 14 days) in men and women. The population was men and women with first time primary syphilis and HIV negative. The BPG arm had 420 participants whilst the doxycycline/tetracycline arm had only 25 participants and numbers of doxycycline or tetracycline not given. The evidence suggested that there was no difference in serological response reported between 6 and 24 months (1 study, very low quality).

Adverse events, clinical cure, compliance and antimicrobial resistance were not reported.

Ceftriaxone 1g IM daily for 15 days vs procaine penicillin 2.4 million units IM daily with probenecid 500mg by mouth for 15 days

One very small RCT[75] comprising 31 participants evaluated syphilis treatment with ceftriaxone (1 g IM daily for 15 days) compared to procaine penicillin (2.4 million units IM once a day) with probenecid (500mg orally four times daily for 15 days) in men and women. The population was patients with HIV and asymptomatic syphilis (presumably late latent syphilis). The majority of participants were men with 81% in the penicillin group and 93% in ceftriaxone group. The evidence suggested that there was no difference in serological response and adverse events between groups (1 study, very low quality evidence). However, the evidence suggested that the ceftriaxone may provide a benefit in increased number with serological response without subsequent relapse compared to procaine penicillin with probenecid (1 study, very low quality). Conversely, the evidence suggested that the procaine penicillin with probenecid may provide a benefit in reduced treatment failure (1 study, very low quality).

Clinical cure, compliance and antimicrobial resistance were not reported.

OTHER COMPARISONS

Azithromycin 2g single oral dose vs azithromycin 4g given orally 2 x 2g doses 6-8 days apart

One small study[71] with 3 arms comprising 74 participants evaluated BPG (2.4 million units IM in Birmingham or 2.4 million units IM twice 7 days apart in New Orleans), azithromycin 2g (orally single dose) and azithromycin 4g (orally 2 x 2g doses 6-8 days apart) in men and women. The population was patients with early (primary, secondary or early latent) syphilis and 4% were HIV positive. The study reported that 57% (12/21) were male in BPG group,

62% (13/21) in azithromycin 2g group and 50% (16/32) were male in azithromycin 4g group.

When comparing the two azithromycin arms, the evidence suggested that 2g dose of azithromycin may provide a benefit in increased number with serological response at 3, 6, 9 and 12 months (1 study, very low quality) compared to 4g dose.

Clinical cure, adverse events, compliance and antimicrobial resistance were not reported.

Minocycline 2 weeks (100 mg orally, twice daily, for 14 days) vs minocycline 4 weeks (100 mg orally, twice daily, for 28 days)

One observational study[83] with 3 arms comprising 196 participants evaluated minocycline 2 weeks (100mg orally, twice daily for 14 days) compared to minocycline 4 weeks (100mg orally, twice daily for 28 days) compared to BPG (2.4 million units IM) in men and women. The population was men and women without HIV with a first time diagnosis of early syphilis (primary, secondary or early latent stages).

When comparing the two minocycline arms, the evidence suggested the minocycline 4 week dose may provide a benefit in increased number with a serological response at 2 years (1 study, very low quality). However, the evidence suggested that there was no difference in serological response at 1 year (1 study, very low quality).

Adverse events, clinical cure, compliance and antimicrobial resistance were not reported.

BPG triple dose (2.4 million units IM three times over 3 weeks) vs BPG single dose (2.4 million units IM once)

One small RCT[76] comprising 64 participants evaluated syphilis treatment with a triple dose of BPG (7.2 million units given as 2.4 million units IM three times over 3 weeks) compared to a single dose of BPG (2.4 million units IM given once) in men and women. The population was patients with HIV and untreated early syphilis (primary, secondary or early latent). The majority of participants were men with only 5% women enrolled. 81% of the study population reported as men who have sex with men (MSM). The evidence suggested that the triple dose of BPG may provide a benefit in increased number with serological response compared to the single dose (1 study, very low quality). The evidence suggested that there was no difference in adverse events (1 study, very low quality).

Clinical cure, compliance and antimicrobial resistance were not reported.

Two observational studies[80, 86] comprising of 60 and 570 participants evaluated syphilis treatment with a triple dose of BPG compared to a single dose of BPG in men and women. One of the observational studies[80] comprising of 60 participants with HIV and untreated syphilis (early syphilis). The majority of participants were men (94%) and 47% in one arm and 40% in the other arm of the study population reported as MSM. The other observational study[86] comprising of 570 participants with HIV and early syphilis (primary, secondary or early latent). The majority of participants were men and over 94% reported as MSM. The evidence suggested that there was no difference in increased number with serological response at 3 and 6 months (1 study, very low quality). However, the evidence suggested that the triple dose of BPG may provide a benefit in serological response at 12 months (2 studies, low quality). Clinical cure, compliance and antimicrobial resistance were not reported.

3.16.3.2 Conclusions: Treatment of syphilis in men and women (mixed population)

TREATMENT COMPARISONS WITH PENICILLIN BASED TREATMENT

Combination of BPG treatments vs BPG

The evidence suggested that there was no difference in treatment failure between combined treatment (BPG + amoxicillin + probenecid) compared to standard treatment (BPG). However, there were more cases of diarrhoea in the combined therapy compared to BPG.

The RCT evidence of combined treatment consisting of BPG + ceftriaxone/doxycycline group may provide a benefit in increased number with serological response at 3, 6 and 12 months compared to the BPG group. The evidence suggested that there was no difference in adverse events between the groups.

Azithromycin vs BPG

The RCT evidence suggested that there was no difference in serological response. The evidence suggested that the BPG may provide a benefit in few cases of the gastrointestinal events, nausea and diarrhoea. However, the evidence suggested that there was no difference in vomiting and an increase in Jarisch-Herxheimer events in the BPG group.

The observational evidence suggested that there was no difference in serological response at 12 months.

Ceftriaxone IV vs BPG

The RCT evidence suggested that intravenous ceftriaxone may provide a benefit in increased number with serological response compared to BPG at 6, 9 and 12 months. However, the evidence suggested no difference in serological response at 14 days or at 3 months, adverse events (serious adverse events or drug related), non-cure as serofast at 12 months or clinical cure defined as skin lesions disappeared within one month. There were more cases of probable Jarisch-Herxheimer in the ceftriaxone group compared to BPG group.

Minocycline vs BPG

The observational evidence suggested there was no difference in serological response at 2 years between BPG and minocycline.

Doxycycline vs BPG

The observational evidence suggested that there was no difference in serological cure at 3 months, 9 months and 12 months between BPG and doxycycline. However, there was a benefit of more cases of serological cure at 6 months with BPG compared to doxycycline.

Doxycycline/tetracycline vs BPG

The observational evidence suggested that there was no difference in serological response reported between 6 and 24 months.

TREATMENT COMPARISONS WITH PENICILLIN G PROCAINE

The RCT evidence suggested that the ceftriaxone may provide a benefit in increased number with clinical cure defined as subsidence of skin lesions after one week compared to penicillin G procaine. However, the evidence suggested that there was no difference in serological response or non-cure described as incidence of seroresistance.

The RCT evidence suggested that there was no difference in serological response or adverse events between ceftriaxone compared to procaine penicillin with probenecid. However, the evidence suggested that the ceftriaxone may provide a benefit in increased number with serological response without subsequent relapse compared to procaine penicillin with probenecid. Conversely, the evidence suggested that the procaine penicillin with probenecid may provide a benefit in reduced treatment failure compared to ceftriaxone.

Dose comparison of azithromycin

The RCT evidence suggested that 2g dose of azithromycin may provide a benefit in increased number with serological responses compared to 4g dose of azithromycin.

Dose comparison of minocycline

The observational evidence suggested the minocycline 4 week dose may provide a benefit in increased number with serological response at 2 years. However, the evidence suggested that there was no difference in serological response at 1 year.

Single dose BPG vs triple dose of BPG

The observational evidence suggested that there was no difference in serological response at 3 and 6 months but the triple dose of BPG may provide a benefit in increased serological response at 12 months. There was no difference in adverse events.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Resistance to macrolides this includes azithromycin is 100% in Belgium.[119] Parenteral observed treatment is preferred over oral treatment as treatment of choice for better adherence: • To maximize adherence with recommended therapies and reduce complications and transmission, medication for syphilis infection should be provided on site and directly observed. • If medications are not available when treatment is indicated, linkage to an STI treatment facility should be provided for same-day treatment The intramuscular injections are painful and it is advised to administer BPG 2.4 million units by two injections of 1.2 million units in separate places (e.g. each buttock or each thigh muscle – no other muscle) and replacing part of solvent by the same volume of 1% lidocaine solution (to check the solvent first as it may already contain lidocaine). A syringe should be prepared and injected before the second one is prepared and injected. It is advisable not to shake the syringe but to roll the mixture between the hands in order to warm up the product and facilitate its dissolution Advise the patient to walk for 30 minutes (this action will help the product to resorb into the muscle). Doxycycline should not be taken in pregnancy. Doxycycline is known for its photo toxicity risk and the use of high sun protection factor (SPF) broad-spectrum sunscreen is needed to offer good protection against UVB and UVA wavelengths; clothing, hat and behavioural avoidance of sun including shade are also important.[120] Doxycycline can give digestive disorders, in particular oesophageal ulcerations Therefore, doxycycline tablets must be swallowed during the meal with a large glass of water (100 ml) and it is important not to lie down for an hour after taking the tablets.
Quality of evidence	In general, long acting BPG 2.4 million units is the first choice treatment, providing a treponemicidal penicillin level in blood for up to 21–28 days. With daily parenteral treatment with procaine penicillin, a ‘safety margin’ is obtained by giving courses lasting 10–14

	days in early syphilis and 10–21 days in late syphilis. However, well-controlled clinical data are lacking on the optimal dose, duration of treatment and long-term efficacy of all antimicrobials, even for penicillin. [11] There is low quality evidence for benefits and harms of any therapy. Treatment recommendations are based mainly on laboratory considerations, biological plausibility, practical considerations, expert opinions, case studies and past clinical experience.[11] Update literature search: 9 RCTs with very low to low quality evidence and 9 observational studies with very low to low quality evidence.
Costs (resource allocation)	IV applied medication is costly as it requires a hospital stay. Procaine penicillin requires multiple injections and is costly for patient and staff. IM penicillin is cheap. The long-acting formulation BPG is the only drug to treat and to prevent mother-to-child transmission. Unfortunately, shortage of BPG is widespread including several European countries (Nurse-Findlay). BPG shortages were attributable to shortfalls in supply, demand, and procurement in the countries assessed. Issues around supply and demand stem from the very low cost of the off-patent BPG (below 1€) versus the high quality requirements needed to produce an IM drug, making the drug economically unattractive for pharmaceutical industries. Sometimes manufacturers force minimum order quantities. At the present time Belgium imports BPG from Portugal (Lentocillin S 1200) with an unlimited waiver. The federal agency for medicines and health products (FAMPH) started a procedure for Penadur® (Vesale pharma Belgium) to be on the market again.
Patients values and preferences	No studies were found that assessed patient values and preferences, acceptability, equity or feasibility specific to syphilis infections. Procaine penicillin is not considered first line treatment due to the pain related to daily IM injections. IV applied medication is cumbersome for the patient. The IM route can be used in primary care settings but a prescription and extra consultation may be required before administration is done. To reduce pain by injection 1% lidocaine is widely used as an alternative diluent to water for injections. This is not licensed. Some health-care providers are, in practice, averse to providing injections, and additional labour time and costs are associated with IM administration. There is probably no variability in the values people place on the outcomes. However, IM injection may be less desirable among patients than oral administration, and IV therapy is even less likely to be preferred. Compliance with daily intramuscular injections with procaine penicillin has been shown to be good in the United Kingdom.[121]

Table 55 – Syphilis medication prices and availability in Belgium

Antibiotic	BCFI		Public price (in €)	Out-of-pocket payment (in €)
Benzathine benzylpenicilline (BPG)$	Penadur LA*	2 x 1.2 million Units IM in powder for reconstitution Public	2 x 20.16	0
	Penadur LA*	2 x 1.2 million Units IM in powder for reconstitution Hospital	2 x 20.16	Included in hospital forfait: Daily drug price of 0.16
	$Current status stock out problems in Belgium: Vesale Pharma has obtained a waiver in 2016 to import BPG from abroad. In 2016, 6000 vials of Lentocillin® S 1200 were imported from Portugal. This brand has lidocaine as a solvent and the IM injection is therefore experienced as less painful. Other brands are: Retarpen® in Austria, Benzetacil® in Spain, and Sigmacillina® in Italy.			
Doxycycline	Doxycycline EG	10 x 100mg oral	6.86	1.54
	Doxycycline Sanchoz	10 x 100mg oral	6.86	1.54
	Vibratab	10 x 100mg oral	6.86	1.54
	Doxylets	10 x 100mg oral	6.94	1.61
Ceftriaxone	Mylan	Hospital 1 x 1 g IM (powder + solvent)	4	4
	Mylan	Hospital 1 x 1 g IM (powder + solvent)	44	44
	Fresenius Kabi	10 X 1 g IM	56.61 (BCFI recommended 'cheap')	11.90
	Sandoz	Hospital 10 x 1 g IM	47	47
	Rocephine	1 x 1 g with 3.5 ml solvent	10.72	2.47 or 1.63

**Criteria for full reimbursement (http://www.bcfi.be/nl/ampps/23176?cat=a). The prescription will be checked by the doctor of the patient's insurance sickness fund and is valid for one year. The patients has either 1. a positive syphilis serology as documented in the patient's medical file OR 2. Is the partner of a patient with syphilis. Maximum reimbursement frequency rules: 6 times 1.2 million Units per year.*

3.16.4 Recommendations for treatment of syphilis in women and men and young people (excluding pregnant women)

Treatment of syphilis in women and men including young people excluding pregnant women	Strength of Recommendations	Level of Evidence
Early syphilis		
Give the following treatment to adults and adolescents with early syphilis (primary, secondary and early latent up to 1 year) including HIV positive patients:		
• First choice: BPG 2.4 million units at once intramuscularly on day 1	Strong	Low
• Second choice: Doxycycline 100 mg orally twice daily for 14 days (be aware of photosensitisation)	Strong	Very low
Late syphilis		
Give the following treatment to adults and adolescents with late syphilis (> 1 year), including HIV positive patients:		
• First choice: BPG 2.4 million units IM weekly for 3 consecutive weeks (day 1, day 8 and day 15)	Strong	Low
• Second choice: Doxycycline 100 mg orally twice daily for 28 days (be aware of photosensitisation)	Strong	Very low
In case of penicillin allergy		
• When in doubt, first assess the risk of anaphylaxis. If patients have a history compatible with an IgE mediated allergy then alternative therapies (such as doxycycline) should be used.	Strong	Very low
• Patients should also be referred for skin testing to confirm allergy and for consideration of penicillin desensitisation.	Weak	High

3.16.5 Treatment of syphilis: Good practice statements

Treatment of syphilis: Good practice statements
Administer BPG 2.4 million units by two injections of 1.2 million units in separate places (e.g. each buttock) and replacing part of solvent by the same volume of 1% lidocaine solution may reduce the pain associated with injection; check the solvent first as it may already contain lidocaine. Advise the patient to walk for 30 minutes to help the product resorb into the muscle.
Physicians should warn patients of the photo toxicity risk associated with doxycycline and advise patients on the use of a high sun protection factor (SPF) broad-spectrum sunscreen that offers good protection against UVB and UVA wavelengths; clothing, hat and behavioural avoidance of sun including shade are also important.
How to take doxycycline? • the tablets must be swallowed during the meal with a large glass of water • it is important not to lie down for an hour after taking the tablets. These conditions of intake must be respected due to possible digestive disorders, in particular oesophageal ulcerations.

3.17 Treatment of uncomplicated syphilis in case of allergy to penicillin

There was no studies identified comparing syphilis treatment for people with allergy to penicillin. For this specific group of patients, the discussion and recommendations summarised in the previous section as alternatives to penicillin-based treatment can be applied.

3.18 Test of cure, follow-up and referral for syphilis

3.18.1 Recommendations from international guidelines

3.18.1.1 Test of cure

Table 56 – When to perform a test of cure for syphilis – Definitions from international guidelines

Source	Recommendation for 1st line	Remarks
BASHH 2015[6]	Minimal recommended follow-up is syphilis serology at three, six and 12 months, or until serofast (no decrease or increase of serology levels): 1D.	Clinical and serological (non-trep RPR) follow-up should be at three, six and 12 months. Referral is indicated when titres do not decrease four-fold within 12 months of therapy. Treatment failure is likely when - Four-fold or greater titre increase in non-treponemal titre - Recurrence of signs or symptoms - Re-infection excluded Patients need to be referred in case of treatment failure or re-infection. Lifelong annual syphilis serology is indicated in patients with HIV.
IUSTI 2014[11]	Follow-up to ascertain cure and detect reinfection or relapse is achieved by assessing the clinical and serological response to treatment.	**Early syphilis:** minimum clinical and serological (VDRL/ RPR) at 1, 3 months then at 6 and 12 months. - After treatment of early syphilis the titre of a NTT (e.g. VDRL and/or RPR) should decline by two dilution steps (fourfold) within 6 months (this is however not the case in ≥ 15% of patients with early syphilis and no HIV infection). - If a fourfold decrease of the titre of a NTT does not occur after 6–12 months, some experts recommend additional treatment with one weekly injection of BPG 2.4 million units for 3 weeks [IV; C]. - A negative NTT can be obtained in a substantial (but not in all) number of patients treated for early syphilis after 1– 2 years. A negative NTT after treatment is considered as the best test of cure. - A TT may remain positive for life following effective treatment; proper documentation is necessary to prevent unnecessary retreatment. **In late (latent) syphilis:** the serological response of NTTs is often absent. In non-HIV-infected late latent syphilis patients with a reactive NTT, which remains stable in the lowest titre range, follow-up after treatment is generally not indicated.

	Reinfection: An increase in ≥2 dilution steps (fourfold) in a NTT suggests reinfection or reactivation. Treatment should be given according to the above guidelines. Reinfection or relapse should be retreated preferably with supervised treatment schedules to ensure compliance and sexual partners should be rescreened.

3.18.1.2 Intervals of testing for follow-up

Table 57 – Conclusions and recommendations from guidelines – Follow-up

Source	Recommendation for 1st line
IUSTI 2014[11]	Testing for serological activity and monitoring of treatment: • Quantitative VDRL or RPR tests may both be used for monitoring the disease progression and effectiveness of treatment at follow-up visits. • Titre must be obtained on the very first day of treatment, that is, to provide a baseline for measuring a decrease in antibody titres. • Serum should be obtained at 1, 3 and every 6 months subsequently, ideally the identical NTT should be used and all samples tested in the same laboratory. This should be continued until the NTT becomes negative, attains a low plateau (1 :1 –1 : 4, sustained for 1 year and in the absence of ongoing risk). Patients with higher titres should remain under follow-up Repeat negative serological tests for syphilis (STS): • At six and 12 weeks after an isolated episode which is high risk for exposure to syphilis, • At two weeks after possible chancres that are dark-ground and/or PCR negative are observed: 1B.
BASHH 2015[6]	Repeat screening is recommended • Six and 12 weeks after a single 'high risk' exposure (unprotected oral, anal or vaginal intercourse with homosexual man, multiple partners, anonymous sex in saunas and other venues, commercial sex worker or sex partner linked with a country where the prevalence of syphilis is known to be high). • In individuals at ongoing risk due to frequent 'high risk' exposures as defined above, screening as part of routine sexual health check-ups for all STIs including HIV and others is recommended, usually every three months and informed by sexual history. • Two weeks after presentation in those with dark field or PCR negative ulcerative lesions that could be due to syphilis

3.18.1.3 Referral to infectious disease or other specialist

Table 58 – Conclusions and recommendations from guidelines – Referral

Source	Recommendation for 1st line
IUSTI 2014[11]	A person with positive serological test for syphilis should be investigated and treated as for syphilis as a precautionary measure unless previously adequately treated syphilis is documented.
BASHH 2015[6]	Patients with neurological, cardiovascular or ophthalmic involvement should be referred for a full evaluation to the respective specialist. The respective gynaecologist, midwife, and paediatrician (or multi-disciplinary team) should be informed whenever a pregnant patient presents with a syphilis diagnosis in order to start up a birth plan.

3.18.2 Recommendations regarding follow-up of a treated patient

Follow-up of patients with treated syphilis	Strength of Recommendations	Level of Evidence
In case of a positive serology:		
1. Clinical and serological (non-trep RPR) follow-up should be performed • for early syphilis at three and six months • for late syphilis at three, six and 12 months	Strong	Very low
2. Referral [μ] is indicated when • recurrence of signs or symptoms • when RPR titres do not **decrease** four-fold within 6 months from day 1 of treatment for early syphilis (primary, secondary and early latent <1 year) • when RPR titres do not decrease four-fold within 12 months from day 1 of treatment for late syphilis (> 1 year**)**	Strong	Very low
In case of negative results (serum or PCR) in a suspected infected patient:		
1. Symptomatic patients with ulcer(s) treated for syphilis: • repeat serologic tests at 6 weeks after ulcer appearance to exclude diagnosis • optionally, perform serologic tests at 2 weeks after ulcer appearance to exclude diagnosis	Weak	Very low
2. Asymptomatic patients after an isolated high risk episode with exposure to syphilis: • repeat serologic test at 6 weeks (in all cases) • and at 12 weeks (optionally) after treatment according to laboratory procedures.	Weak	Very low

[μ] *Referral to the appropriate specialist or medical colleague knowledgeable in syphilis who consults at a dedicated STI / HIV clinic or an infectious disease clinic or hospital*

3.18.3 Testing frequency for syphilis: Good practice statements

Testing frequency for syphilis: Good practice statements
Repeat testing interval every 3 to 12 months (same for other STIs) for asymptomatic patients with high risk sexual behaviour or at increased risk for syphilis: 1. Sex worker of any gender 2. MSM with high risk behaviour • unprotected sexual contacts (including deep kissing) in non-exclusively monogamous relationships • who are on PrEP • with a recent HIV diagnosis • with a syphilis diagnosis in the past A negative result will act as a baseline for future testing.

3.19 Notification of syphilis

3.19.1 Recommendations from international guidelines

Source	Recommendation for 1st line
IUSTI 2014[11]	Notification of syphilis to the relevant authority is mandatory in most European countries, particularly early syphilis and congenital syphilis. The ECDC is responsible for the European Union-wide surveillance of communicable diseases including syphilis.

3.19.2 Mandatory notification of syphilis

All cases of infections by syphilis have to be notified in Brussels and Flanders using one of the three channels offered to healthcare practitioners to notify an infectious disease (phone, mail or website).

4 IMPLEMENTATION

4.1 Implementation of the scientific report document

The scientific report or guideline will be posted on the KCE website at the moment of publication. It will be accessible to professionals and the general public. Both the full main report and the supplement with appendices together make up the scientific report and are written in English.

A summary in French, Dutch and English is published together with the scientific report. The summary is aimed at the primary care practitioners and the general public.

The report is forwarded to all stakeholders and GDG members who participated in de the development of the guideline. Further, the report and summaries are provided to all other identified stakeholders and their respective associations. The GDG and stakeholders that were involved in the development have already expressed their commitment to take the recommendations forward to their associations and apply them into their own local tools and guidance.

4.2 Translating the guideline into a primary care sexual health consultation STI testing tool

To implement this guideline in the daily clinical practice of health care providers, and to answer to decrease the so-called “knowledge-to-action gap”, i.e. the (lack of) translation of research findings into practice, a sexual consultation tool for STI testing is currently under development. The stakeholders and GDG were in favour of the development of a guidance tool as described below.

4.2.1 Clinical guidance

The amount of guidelines and tools available online reflects that international guidance already exists. The members of the GDG group emphasised the need for a hands-on tool, easy to use during the consultation with the patient, to guide them quickly in identifying which patient should be approached for STI testing. The objective being to better identify and target the patient and patient groups with the highest likelihood of being positive for an STI. In order to define the patient or groups to be targeted for testing in primary care, the input from the GDG and stakeholders with a broad background was consulted (see colophon).

The ideal guidance helps the physician with identifying which test, the correct treatment in case of a positive test result and the best way to follow up the patient. In short, the focus was on guiding the primary caregiver on the different steps in a sexual health consultation, for the detection and treatment of STIs (including HIV).

Domus Medica previously developed a sexual health consultation tool as a paper version but an update of the clinical information was due.[19] The scoping group and GDG preferred a paper version to be supplemented with an electronic version of the guidance tool. It was decided at the stakeholders meeting that a search in the (grey) literature had to be performed to identify well performing online ‘interactive dynamic’ tools or ‘static’ sexual health consultation tools. With the help of experts of the GDG and a critical analysis of the retrieved documents, it was decided to create a new tool.

4.2.2 Overview of guidance documents

Several organisations across Belgium involved in STI care had developed guidance and patient leaflets for their own use. Unfortunately a tool in which all sources of information were gathered, was lacking. The GDG emphasised the importance of a clear overview of the different steps for STI testing in a sexual health consultation in primary care. The tool had to summarise the newly developed guidelines on chlamydia, syphilis and gonorrhoea, but moreover to refer to information from other sources, such as the website of stakeholders (SIDA’SOS, Sensoa), medical organisations (Domus Medica, SSMG), etc.

A critical analysis of existing guidance and tools defined the structure and identified intermediary steps as a basis for a sexual health STI consultation tool in primary care. The guidance documents and tools that were retrieved and reviewed are described in Table 59.

Table 59 – STI consultation tool: overview of international and national guidance documents

Guidance documents, tools and websites	
Belgium	
Domus Medica 2017 - SOI[14]	https://www.domusmedica.be/documentatie/downloads/praktijkdocumenten/richtlijnen/1332-praktijktool-seksueel-overdraagbare-infecties-aanpak-in-de-huisartsenpraktijk.html
Domus Medica 2017 - HIV screening[122]	https://www.domusmedica.be/documentatie/downloads/praktijkdocumenten/steekkaarten-en-andere-hulpmiddelen/b-bloed-bloedvormende-organen-en-immuunstelsel/1328-advies-hiv-screening-door-huisartsen.html
Ghapro 2014 - Sex workers[15]	http://www.ghapro.be/nl/ghapro-publicaties_andere.html
BAPCOC 2012 - first line[123] **BAPCOC 2017 - hospital**[18]	http://overlegorganen.gezondheid.belgie.be/nl/advies-en-overlegorgaan/commissies/BAPCOC
Europe	
IUSTI 2012 – Consultation for STIs[124]	https://iusti.org/regions/Europe/euroguidelines.htm
The Netherlands 2013 – SOA consult[125]	https://www.nhg.org/standaarden/samenvatting/het-soa-consult
The Netherlands 2018 – Dermatology[126]	https://www.nhg.org/sites/default/files/content/nhg_org/uploads/multidisciplinaire_richtlijn_soa_herziening_2018.pdf
UK BASHH 2013 – national guideline for consultations requiring sexual history taking[127]	https://www.bashh.org/guidelines
UK BASHH STI 2015 – testing STI[128]	https://www.bashh.org/guidelines https://www.bashhguidelines.org/media/1084/sti-testing-tables-2015-dec-update-4.pdf
International	
Australia 2017 online[129]	https://stipu.nsw.gov.au
Australia 2014 – MSM[130]	https://www.clinicalguidelines.gov.au/portal/2489/australian-sexually-transmitted-infection-and-hiv-testing-guidelines-2014-asymptomatic
Australia 2017 – Silverbook[131]	http://ww2.health.wa.gov.au/Silver-book; https://stipu.nsw.gov.au/wp-content/uploads/STI-HIV-Testing-Tool-online.pdf
US CDC 2015[23]	https://www.cdc.gov/std/tg2015/default.htm
Canada 2010 & 2016 – STI guideline[132, 133]	https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections.html

4.2.3 Structure of the STI consultation tool

The tool that was preferred and selected by the GDG was the nicely conceptualised online tool for an STI consultation proposed by the Australian New South Wales government: “STI/HIV testing tool: easy as 1 2 3” updated in September 2017 (https://stipu.nsw.gov.au/wp-content/uploads/STI-HIV-Testing-Tool-online.pdf).

The main reasons for the choice were: the scope of the tool, its applicability to the Belgian situation, the clarity of presentation, its recent update and the yearly revision of the tool. This tool covers three main topics answering the following questions: ‘Starting a conversation about sexual health testing’; ‘STI/HIV testing table (describing the patient and specific risk groups for STIs)’; ‘How to test – Infection, specimen site and test type’; ‘Contact tracing’. The tool is set in such a way that it lists for each of the groups at risk, the commonly encountered infections and the timeframe how often the patient should be tested. The specimen collection site is further described by gender for each infection including the preferred test.

During the elaboration of the tool and regular discussions with the GDG, several aspects were considered as key elements of the tool. These aspects could be related to the content, for example the definition of the groups at risk, but also more design related aspects were highlighted by the GDG members e.g. the linkage with the existing sources of information on STIs in Belgium.

The GDG preferred a Belgian tool to have a chronological order as for a normal consultation, as follows:

- starting with how to breach the sexual health topic during a consultation with the patient,
- how to assess the risk for an infection with an STI,
- which test to perform,
- how to treat the STI,
- if a test of cure is required,
- further follow-up of the patient,
- and the management of the partner of the patient.

Next to the management of the patient, general tools and information should be available to inform the patient on STIs in general.

The final structure of the consultation tool will therefore follow the following suggested structure in Table 60.

Table 60 – An STI consultation tool: proposed structure

Structure of the tool	
STEP 1	**Starting a conversation about sexual health testing**
STEP 2	**Sexual history questions for readiness, needs and risk assessment**
STEP 3	**STI Testing overview**
STEP 4	**How to test**
STEP 5	**Treatment overview - Test of cure - Follow up**
STEP 6	**Partner management and contact**

An example of a draft of the consultation tool is available in Appendix 11. The final development of the tool (paper and online version) will be part of a second KCE project and therefore the final results are not presented here.

4.3 Policy and other implementation of this guideline

4.3.1 Barriers and facilitators

During the GDG and stakeholders meetings, barriers and facilitators related to the use of this guideline were brought up. As presented above, an online tool was seen as a strong facilitator. The set-up and final result of the tool will be further elaborated in a follow up project at KCE in 2019.

An identified barrier was the nomenclature and reimbursement for diagnostic tests with NAATs and gonorrhoea culture for resistance testing and surveillance. During the development of the guideline, KCE experts with members of the GDG shared this concern with RIZIV – INAMI representatives. The following eventual policy implications of the guideline for INAMI/RIZIV were discussed:

- Is it possible to introduce a new nomenclature code for reimbursement of a combi NAAT chlamydia/gonorrhoea test in addition to the separate nomenclature codes for the diagnosis of gonorrhoea and chlamydia,
- The reimbursement modalities for the combi NAAT test need further discussions between NIHDI and experts from the field (including representatives of laboratories and clinical specialists treating STI, and representatives of main patients STI associations) in order to be revised

The anticipated effect of the guideline was reflected on together and the identified issues will be taken forward to the microbiology working group by RIZIV – INAMI.

An important facilitating aspect for this guideline is the existence of the working group across governmental cabinets (‘Inter-kabinetten Werkgroep’ or ‘Groupe de travail inter-cabinets’) which was installed to coordinate the governmental actions for STIs and HIV. The KCE project was presented to this group in 2017 for input and feedback.

The Flemish government invited the KCE to a panel discussing the new Flemish actions for sexual health on December 14th 2018. The broad audience was informed of the guideline and its planned date of release. The Flemish Agency ‘Vlaams Agentschap Zorg en Gezondheid’ is currently rolling out the online partner notification (partneralert.be) and in this context the guideline will be applied.

The Belgian Antibiotic Policy Coordination Committee (BAPCOC), a federal instance that is highly scientifically based aiming to promote rational antibiotics consumption and to fight the increase of antibiotics resistance, expressed its interested to apply the treatment recommendations to the guideline for primary care (personal communication Prof De Sutter). This guideline is in alignment with the ‘policy paper for the 2014-2019 term’ (available at https://consultativebodies.health.belgium.be/en/documents/policy-paper-bapcoc-2014-2019).

4.3.2 Actors

As discussed already above, the implementation of this guideline and the online tool will be facilitated/conducted by SENSOA and SIDA'SOS (e.g. professional associations). Several associations expressed an interest for the results to be presented to their local group of practitioners. SENSOA plans to promote the guideline through their website sensoa.be, through the SENSOA newsletter and the implementation project 'onder4ogen' which teach the general physician to talk about sexual health. SENSOA will further promote the guideline through their stakeholders and the Flemish STI consortium (Vlaams SOA Overleg).

On the other hand the content of this guideline is intended to be disseminated by scientific and professional organisations. Domus Medica will promote both this guideline and the chlamydia guideline as part of the existing sexual health topic online for primary care physicians. The guideline will be placed on the 'evidence based practice' website in Dutch and French (https://www.ebpnet.be). Organisations can make attractive and user-friendly tools tailored to caregivers groups. They will also play a key role by a dissemination that makes use of diverse channels such as websites or sessions of continuing education e.g. laboratory education by the reference ITM laboratory, STI education sessions for GPs, presentation of prevalence and surveillance gonorrhoea and other STI data by Sciensano.

5 GUIDELINE UPDATE

In view of the rapidly evolving evidence, this guideline should be updated every 5 years. If, in the meantime, important new evidence would become available, this should be taken into consideration.

The KCE processes foresee that the relevance of an update would be yearly assessed for each published guideline by the authors. Decisions are made on the basis of new scientific publications on a specific topic (e.g. Cochrane reviews, RCTs on medications or interventions). Potential interest for groups of health practitioners is also considered in this process.

This appraisal leads to a decision on whether to update or not a guideline or specific parts of it to ensure the recommendations stay in line with the latest scientific developments.

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