Evaluatie van universele en doelgroep hepatitis A vaccinatie opties in België

KCE reports vol. 98A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
2008

Het Federaal Kenniscentrum voor de Gezondheidszorg

Voorstelling : Het Federaal Kenniscentrum voor de Gezondheidszorg is een parastatale, opgericht door de programma-wet van 24 december 2002 (artikelen 262 tot 266) die onder de bevoegdheid valt van de Minister van Volksgezondheid en Sociale Zaken. Het Centrum is belast met het realiseren van beleidsondersteunende studies binnen de sector van de gezondheidszorg en de ziekteverzekering.

Raad van Bestuur

Effectieve leden : Gillet Pierre (Voorzitter), Cuypers Dirk (Ondervoorzitter), Avontroodt Yolande, De Cock Jo (Ondervoorzitter), De Meyere Frank, De Ridder Henri, Gillet Jean-Bernard, Godin Jean-Noël, Goyens Floris, Kesteloot Katrien, Maes Jef, Mertens Pascal, Mertens Raf, Moens Marc, Perl François, Smiets Pierre, Van Massenhove Frank, Vandermeeren Philippe, Verertbruggen Patrick, Vermeyen Karel.

Plaatsvervangers : Annemans Lieven, Bertels Jan, Collin Benoît, Cuypers Rita, Decoster Christiaan, Dercq Jean-Paul, Désir Daniel, Laasman Jean-Marc, Lemye Roland, Morel Amanda, Palsterman Paul, Ponce Annick, Remacle Anne, Schrooten Renaat, Vanderstappen Anne.

Regeringscommissaris : Roger Yves

Directie

Algemeen Directeur a.i. : Jean-Pierre Closon

Adjunct-Algemeen Directeur a.i. : Gert Peeters

Contact

Federaal Kenniscentrum voor de Gezondheidszorg (KCE)
Administratief Centrum Kruidtuin, Doorbuilding (10e verdieping)
Kruidtuinlaan 55
B-1000 Brussel
Belgium

Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85

Email : info@kce.fgov.be
Web : http://www.kce.fgov.be

Evaluatie van universele en doelgroep hepatitis A vaccinatie opties in België

KCE reports 98A

PHILIPPE BEUTELS, JEROEN LUYTEN, OLIVIER LEJEUNE, NIEL HENS,
JOKE BILCKE, KOEN DE SCHRIJVER,
STEFAAN VAN DE SANDE, KOEN VAN HERCK,
PIERRE VAN DAMME

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
2008

KCE REPORTS 98A

Titel :	Evaluatie van universele en doelgroep hepatitis A vaccinatie opties in België
Auteurs :	Philippe Beutels (Universiteit Antwerpen, UA), Jeroen Luyten (UA), Olivier Lejeune (UA), Niel Hens (Universiteit Hasselt), Joke Bilcke (UA), Koen De Schrijver (UA), Stefaan Van de Sande (KCE), Koen Van Herck (UA), Pierre Van Damme (UA)
Externe experts :	Kristina Bosmans (IDEWE), André Elewaut (UZ Gent), Patrick Goubau (Cliniques Universitaires Saint-Luc, Brussels), Yves Horsmans (Cliniques Universitaires Saint-Luc, Brussels), Beatrice Swennen (Université Libre de Bruxelles), Marc Van Ranst (Katholieke Universiteit Leuven).
Externe validatoren :	Maarten J Postma (RU Groningen, The Netherlands), Hans Van Vlierberghe (UZ Gent), Sophie Quoilin (Institute for Public Health, Brussels)
KCE experts :	Frank Hulstaert, Michel Huybrechts
Conflict of interest :	Prof dr Philippe Beutels, drs Jeroen Luyten, dr Olivier Lejeune, Prof dr Niel Hens, drs Joke Bilcke hebben geen belangenconflict te melden. Prof dr Pierre Van Damme en dr Koen Van Herck verklaren dat zij onderzoeker zijn van klinische studies waarvoor de Universiteit Antwerpen onderzoeksbeurzen ontvangt en dat het educatief fonds van de Universiteit Antwerpen speaker-fees ontving voor presentaties die ze gaven over Hepatitis A vaccins, vanwege de firma's die deze produceren.
Acknowledgements:	De auteurs zijn volgende personen bijzonder erkentelijk: alle personen werkzaam onder de supervisie van het "Team Infectieziektes" van het "Toezicht Volksgezondheid" van de Vlaamse Gemeenschap, voor hun inzet bij de recrutering van hepatitis A patiënten voor de bevraging en voor het ter beschikking stellen van de gegevens van de gedetecteerde clusters. We danken daarom het team Infectieziekten van de afdeling Toezicht Volksgezondheid van het Vlaams Agentschap Zorg en Gezondheid, in het bijzonder een groot aantal medewerkers van de equipes in de provincies die we hier niet met naam kunnen vermelden, respectievelijk onder leiding van, Dr Petra Claes, Dr Anmarie Forier, Dr Ruud Mak, Dr Koen de Schrijver en algemeen coordinatoren Dr Emmanuel Robesyn en Dr Geert Top. De auteurs zijn dankbaar voor de toegang tot niet-gepubliceerde gegevens en/of constructief advies en commentaar van Prof dr Peter Michielsen (Universitair Ziekenhuis Antwerpen), Dr Germaine Hanquet, Dr Veronik Hutse (Wetenschappelijk Instituut Volksgezondheid (WIV)), Mr Joachim Deroey (University hospital Leuven), Mr Josée Monard (University hospital Liège), Mrs Francine Roggen (University hospital St Luc, Brussels, Mr Luc Colenbie (University hospital Gent), Mrs Elianne Angenon (University hospital Erasmus, Brussels), Dr Vincent Karam (European Liver Transplant Registry), Prof dr Rene Adam (European Liver Transplant Registry). De auteurs danken Dr Frank Hulstaert en Dr Michel Huybrechts van het KCE voor hun constructief advies en ondersteuning. De financiële ondersteuning voor dit project kwam van het KCE, en van "SIMID", een onderzoeksfonds voor strategisch basisonderzoek van het Instituut voor de aanmoediging van Innovatie door wetenschap en technologie in Vlaanderen (IWT), project nummer 060081, gecoördineerd door Prof dr Philippe Beutels, UA.

Disclaimer: De externe experten hebben aan het wetenschappelijke rapport meegewerkt dat daarna aan de validatoren werd voorgelegd. De validatie van het rapport volgt uit een consensus of een meerderheidsstem tussen de validatoren. Alleen het KCE is verantwoordelijk voor de eventuele resterende vergissingen of onvolledigheden alsook voor de aanbevelingen aan de overheid.

Layout : Ine Verhulst

Brussel, 09 januari 2009

Studie nr 2007-32-1

Domain : Health Technology Assessment (HTA)

MeSH : Hepatitis A ; Hepatitis A Vaccines ; Models, Statistical ; Disease Transmission, Infectious

NLM classification : WC 536

Taal : Nederlands, Engels

Format : Adobe® PDF™ (A4)

Dépôt légal : D/2008/10.273/88

Elke gedeeltelijke reproductie van dit document is toegestaan mits bronvermelding. Dit document is beschikbaar van op de website van het Federaal Kenniscentrum voor de gezondheidszorg.

Hoe refereren naar dit document?

Beutels P, Luyten J, Lejeune O, Hens N, Bilcke J, De Schrijver K, et al. Evaluatie van universele en doelgroep hepatitis A vaccinatie opties in België. Health Technology Assessment (HTA). Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE); 2008. KCE reports 98A (D/2008/10.273/88)



VOORWOORD

Hepatitis A is het mogelijke gevolg van feco-orale overdracht en infectie met het hepatitis A virus. De infectie komt meer voor bij kinderen dan bij volwassenen. De meeste kinderen zullen relatief weinig last ondervinden. Uitzonderlijk kan de ziekte, vooral dan bij volwassenen, erge gevolgen hebben voor de lever.

Vooral een verbeterde hygiëne heeft ertoe geleid dat deze infectie nu minder voorkomt bij ons, en een groot deel van de volwassenen zijn opgegroeid zonder de infectie door te maken. Ze zijn dus ook niet beschermd tegen het virus. Af en toe worden nog clusters van hepatitis A gerapporteerd, soms grootschalig na een voedselinfectie, meestal op kleine schaal in crèches en scholen. De meeste gevallen worden waarschijnlijk niet gerapporteerd, ook al bestaat een verplichting. Sinds 1992 bestaat een vaccin tegen hepatitis A, dat goed verdragen wordt. In een groot deel van de wereld is hepatitis A nog hoog-endemisch en worden reizigers naar die streken aangeraden zich te laten vaccineren.

De veranderende epidemiologische toestand roept vragen op naar de huidige ziektelast door hepatitis A in België en het te volgen vaccinatie beleid.

De gegevens nodig om dit grondig te bestuderen waren niet steeds beschikbaar. We danken hierbij speciaal het “Team Infectieziektes” van het “Toezicht Volksgezondheid” van de Vlaamse Gemeenschap voor het verzamelen van de gegevens en de equipe van de Universiteit Antwerpen voor de kritische analyse en verwerking met een wiskundig model.

Overstappen van een wiskundig model naar praktische beleidsaanbevelingen is niet steeds eenvoudig. We hopen dat de aanbevelingen voortvloeiend uit de studie van nut zullen zijn.

Gert Peeters
Adjunct algemeen directeur a.i.

Jean-Pierre Closon
Algemeen directeur a.i.

Samenvatting

INTRODUCTIE

Wereldwijd zijn er elk jaar ongeveer 1,5 miljoen patiënten met hepatitis A. De ziekte die vooral de lever treft, wordt veroorzaakt door het hepatitis A virus (HAV). De overdracht is feco-oraal. De symptomen bestaan uit koorts, nausea, abdominale pijn en ongemakken, donkere urine, bleke kleur van de feces, en geelzucht (gele verkleuring van de conjunctiva en de huid). De ziekteduur bedraagt een tot drie weken en bijna steeds volgt een volledig herstel. Kinderen die geïnfecteerd raken hebben meestal geen symptomen of de diagnose wordt niet gesteld. Fulminante gevallen zijn zeldzaam en komen vooral voor bij volwassenen. Sinds 1992 zijn een aantal vaccins beschikbaar in België gebaseerd op virus gekweekt in celcultuur en met formaldehyde geïnactiveerd. Deze vaccins worden goed getolereerd en zijn hoogimmunogeen. Ze zorgen voor een langdurige bescherming tegen hepatitis A bij kinderen en volwassenen.

Met uitzondering van levertransplantatie bij fulminante hepatitis A is geen specifieke therapie beschikbaar. De verbetering van de sanitaire voorzieningen en de implementatie van een vaccinatie strategie op nationaal of internationaal niveau hebben geleid tot een substantiële reductie van hepatitis A en de ziektegerelateerde kosten.

Dit KCE project bestudeert de effectiviteit en de kosteneffectiviteit van mogelijke vaccinatiestrategieën in België voor hepatitis A, gebaseerd op de beschikbare epidemiologische gegevens.

RESULTATEN

OMVANG VAN HET PROBLEEM EN EPIDEMIOLOGISCHE GEGEVENS VOOR BELGIË

We hebben de internationaal gepubliceerde literatuur en de grijze literatuur nagekeken, alsook een brede waaier van Belgische gegevens verzameld en geanalyseerd m.b.t. de epidemiologie, de vaccinaties en de kosten. Belgische gegevens zijn cruciaal gezien de variatie per land in de lokale epidemiologie, die verband houdt met verbetering in de sanitaire voorzieningen over de voorbije 80 jaar, het gedrag van de doelgroepen die lokaal voor transmissie zorgen (bvb infectiegevoelige reizigers naar hoog endemische gebieden en bewerkers van voedsel) en het lokaal profylactische gebruik van anti-HAV vaccins en immunoglobulines. De lokale gegevens zijn nodig om de huidige epidemiologische situatie te kunnen begrijpen, en de impact in te kunnen schatten van mogelijke interventies. Een uitgebreid literatuuroverzicht van de economische evaluaties van anti-HAV vaccinatie strategieën toonde aan dat er geen formele economische evaluatie beschikbaar was met voldoende kwaliteit en relevantie voor de Belgische situatie, om antwoorden te geven op de onderzoeksvragen van dit project.

Uit de gerapporteerde gevallen (passief systeem) blijkt dat de incidentie van labgeconfirmeerde gevallen hoogst is bij kinderen onder de leeftijd van 10 jaar, en dit niettegenstaande het feit dat infecties op die leeftijd dikwijls asymptomatisch zijn of enkel aanleiding geven tot vage atypische symptomen, en dus niet frequent gerapporteerd worden via het huidige systeem van surveillantie. Op te merken valt dat we deze cijfers enkel gebruikt hebben voor het uitsluiten van een sterke seizoensgebonden component en voor de validatie van andere bronnen (zie onder) voor de leeftijdsdistributie en de grootte van de onderrapportering. De studie van de clusters van traceerbare gevallen van hepatitis A verzameld door de gezondheidsinspecties in Vlaanderen tonen dikwijls clusters van 2 gevallen, wat erop duidt dat de clusters klein en gelimiteerd blijven.

Minder frequent zijn clusters met meer gevallen bij kinderen die intens contact hebben (bvb in scholen en kindercrèches), en waar de overdrachtketen van persoon tot persoon potentieel langer is alvorens de verspreiding van het virus stopt.

De analyse van alle clusters met een wiskundig model toont aan dat het hepatitis A virus in België hoogstwaarschijnlijk niet endemisch is (het effectief reproductie getal is significant kleiner dan 1, ook na correctie voor een zekere onderrapportering van gevallen). De implicatie van dit lage getal voor effectieve reproductie is dat de huidige epidemiologische situatie in België voor HAV infecties dient verklaard te worden door import van buiten België, en een beperkte verspreiding in zelfuitdovende clusters. Deze import wordt verondersteld vooral plaats te vinden via kinderen van migranten die opgroeiden in België zonder contact met HAV, en die dan als kind (onder de 15 jaar vooral) bij bezoek aan hun familie in een endemisch gebied besmet raken. Meestal blijven kinderen asymptomatisch en bovendien bestaat door de incubatieperiode van ca. 3 weken de kans dat het HAV wordt overgedragen na de terugkeer in België aan andere kinderen die infectiegevoelig zijn, bvb in scholen en kindercrèches.

Simulatie door middel van wiskundige modellen helpt om complexe problemen te begrijpen, en laat toe scenario's uit te werken die niet in de realiteit kunnen getest worden, wegens tijdsgebrek, en ethische of praktische beperkingen. We ontwikkelden wiskundige modellen voor de huidige epidemiologie van het hepatitis A virus in België, en om de medische effecten en de gezondheidskosten in te schatten van het gebruik van de beschikbare anti-HAV vaccins.

Gezien de beperkingen van de routinematig beschikbare surveillantie gegevens voor onze analyses, hebben we ons geconcentreerd op twee datasets (van 1993 en 2002) met seroprevalentie gegevens van de algemene bevolking. Beide datasets zijn samengesteld en eigendom van het Centrum voor de Evaluatie van Vaccinatie (CEV) van de Universiteit Antwerpen. Deze datasets bevatten informatie over immuniteit (een merker voor doorgemaakte infectie eerder dan gerapporteerde ziekte), wat van belang is om de dynamica van de overdacht te modelleren (met inclusie van zowel subklinische alsook niet gerapporteerde infecties). We toonden aan dat het verschil in het seroprevalentie profiel van 1993 en 2002 kan verklaard worden door de demografische evolutie van de bevolking, huidige vaccinatiecijfers en de import van infecties, vooral dan bij kinderen onder de leeftijd van 15 jaar. Dit is dus een bevestiging dat HAV waarschijnlijk niet endemisch is in België.

Met regionale, nationale en internationale beschikbare administratieve gegevens verkregen we schattingen voor het aantal transplantaties en overlijdens, die gepaard gingen met hepatitis A. Het bleek moeilijk het deel te bepalen dat echt kon toegeschreven worden aan hepatitis A, zelfs na consultatie van een groep experts. Dit verklaart de grote onzekerheid rond het aantal overlijdens (die werd meegenomen via probabilistische sensitiviteitsanalyse). Gebruik makend van verschillende bronnen, inclusief een prospectieve bevraging specifiek voor dit project, konden we de ziektelast van hepatitis A voor België inschatten als volgt: 1460 infecties (waarvan 886 met symptomen, daarom niet noodzakelijk gerapporteerd), 60 hospitalisaties per jaar, 1 levertransplantatie per 2 jaar, 2 tot 6 overlijdens per jaar (gemiddeld 3,7). Dit vertaalt zich elk jaar in een verlies van 36 levensjaren en 55 Quality Adjusted Life-Years (QALYs). De directe medische kosten voor behandeling van hepatitis A bedragen gemiddeld €311 000 per jaar, en de totale kosten (inclusief werkverlet) €2.35 miljoen.

KOSTENEFFECTIVITEIT VAN VACCINATIE

Alvorens vaccinatie in rekening te brengen, dient benadrukt te worden dat het onderzoek van de hepatitis A clusters blijvende aandacht vraagt voor de sanitaire voorzieningen die HAV overdracht helpen te vermijden (samen met andere infecties met feco-orale overdracht). Meer bepaald kan het gebeuren dat scholen en crèches niet steeds minimale sanitaire voorzieningen garanderen in toiletten, schoolkeukens en schoolrestaurants. Bovendien hanteren bewerkers van voedsel mogelijks niet steeds de hygiënische voorzorgen bij het bereiden van voedsel. Binnen dit project hebben we echter het belang van zulke maatregelen niet systematisch bestudeerd.

Bij onze analyses gaan we ervan uit dat de sanitaire toestand blijft zoals vandaag en nemen we aan dat vaccins het belangrijkste hulpmiddel zijn om HAV infecties in België te voorkomen. Simulaties werden uitgevoerd om na te gaan hoe effectief en kosteneffectief verschillende hepatitis A vaccinatieopties zijn in België.

We nemen aan dat twee vaccin dosissen nodig zijn, m.a.w. dat het 2-dosissen monovalent HAV vaccin gebruikt wordt (Epaxal® ou Havrix®) en niet het 3-dosissen bivalent hepatitis A – hepatitis B vaccin (Twinrix®), dat niet verenigbaar is met het huidige vaccinatieschema voor Belgische kinderen. We nemen aan dat 1 dosis van het monovalent vaccin geen langdurige bescherming biedt.

Onze simulaties geven volgende resultaten (details zijn weergegeven in onderstaande tabel):

1) Bij een directe kost van ongeveer €200 000 per gewonnen QALY, is anti-HAV vaccinatie van volwassenen niet kosteneffectief in vergelijking met andere gezondheidsinterventies in België, tenzij het volwassenen betreffen die een infectierisico lopen dat vier tot vijf maal hoger is dan dit van een gemiddelde volwassen persoon van dezelfde leeftijd (in dit geval daalt de mediane Incremental Cost-Effectiveness Ratio (ICER) tot minder dan €50 000 per gewonnen QALY). Dit bevestigt dat vaccinatie van bepaalde risicogroepen bij de volwassenen kosteneffectief kan zijn. Deze vaccinatieoptie heeft een verwaarloosbare impact op de epidemiologie van HAV in België, gezien volwassenen niet substantieel bijdragen tot de import van infecties en de lokale overdracht van het virus. Gegeven de huidige prevalentiecijfers, is selectieve vaccinatie van de seronegatieven een optie die functie is van de kosten van het vaccin en de serologische test.

Gebruik makend van de baseline distributies van alle parameters, is het vaccineren van alle volwassenen steeds duurder dan de optie selectief vaccineren na test, maar niet verdedigbaar wegens een te beperkte bijkomende gezondheidswinst. Bij de huidige prijzen en een gemiddelde infectiedruk, is de incrementele kosteneffectiviteit van het veralgemeend vaccineren i.p.v. selectief de seronegatieven niet kosteneffectief aan ongeveer €110 000 per gewonnen QALY. Voor volwassenen met een infectierisico van meer dan drie maal het gemiddelde is dit echter wel een relatieve kosteneffectieve strategie met een mediaan van ongeveer €35 000 per gewonnen QALY. Het blijft een probleem om de grootte van de risicogroepen en het risico juist in te schatten.

2) Anti-HAV vaccinatie van eerste en tweede generatie kinderen van 1 tot 12 jaar (via een catch-up strategie), van ouders of grootouders die migreerden vanuit een hoog-endemisch land naar België, is waarschijnlijk kosteneffectief in vergelijking met de huidige situatie zonder universeel vaccinatie programma. Deze optie kost de gezondheidszorg betaler €11 000 tot €53 000 per gewonnen QALY (en ongeveer €19 000 tot €85 000 per gewonnen levensjaar), afhankelijk van hoe sterk de doelgroep bijdraagt tot de import van HAV infecties in België, vooral bij de kinderen tot 15 jaar.

	Incrementele directe kosten per gewonnen QALY	**Incrementele directe kosten**	**Gewonnen QALYs**
	Mediaan (P5-P95) EURO	Mediaan (P5-P95) Mio EURO	Mediaan (P5-P95)
25% daling van travel import door immigranten doelgroep vaccinatie (1-12j) vs huidige situation	52984 (31038 – 92332)	13,0 (12,5-13,4)	244 (140-417)
75% daling van travel import door immigranten doelgroep vaccinatie (1-12j) vs huidige situation	11607 (6641-20503)	10,0 (8,3-11,3)	859 (494-1457)
Universele zuigelingenvaccinatie (zonder travel import reductie) vs huidige situatie	261519 (155923 – 452295)	303 (301-305)	1171 (677-1964)
Universele zuigelingenvaccinatie vs 75% daling van travel import door immigranten doelgroep vaccinatie (1-12j)	968743 (585190-1750244)	293 (293-294)	310 (172-514)

3) Tegenover de huidige situatie is universele vaccinatie van zuigelingen op de leeftijd van 1 jaar niet kosteneffectief in vergelijking met andere interventies in de Belgische gezondheidszorg, aan €262 000 per gewonnen QALY (en meer dan €400 000 per gewonnen levensjaar). Indien import kan verminderd worden door doelgerichte vaccinatie zoals hierboven beschreven, dan wordt de incrementele kosteneffectiviteit van universele zuigelingenvaccinatie versus de doelgerichte vaccinatie van migrantenkinderen zelfs nog minder attractief (€970 000 per gewonnen QALY). De vaccinatiekosten (aankoopprijs en administratiekost) per gevaccineerde zouden moeten dalen met ca. 70% (inclusief voorkomen werkverlet) of 90% (exclusief voorkomen werkverlet) om te kunnen spreken van een kosten-effectief programma.

DISCUSSIE

Terwijl de beschreven eerste doelgroep vaccinatie optie logisch lijkt in de context van de epidemiologische gegevens, konden we doelgroepvaccinatie van bewerkers van voedsel niet op kosteneffectiviteit evalueren gezien het aantal bewerkers van voedsel niet gekend is, noch hun gemiddelde leeftijd en het verloop naar jobs buiten de voedselbewerking.

Optie twee, hoewel kosteneffectief, kan als meer controversieel beschouwd worden gezien hier de doelgroep bestaat uit kinderen met een specifieke etnische achtergrond, namelijk vooral kinderen van Turkse of Marokkaanse origine. De grootte van deze groep was gekend voor België en werd in het model verrekend. Anekdotische analyses van clusters in België en gegevens uit Amsterdam tonen aan dat deze groep inderdaad vaak aan de basis ligt van circulatie van HAV bij kinderen. Enkel een systematische fylogenetische analyse van de hepatitis A virussen in België kan echter verdere informatie geven i.v.m. hun oorsprong. Er bestaat hier duidelijk nog ruimte voor verder onderzoek. Het succes van zulk een programma is afhankelijk van het feit of HAV infecties echt te wijten zijn aan deze groep kinderen, en of die groep kan geïdentificeerd en bereikt worden op basis van de geboorteplaats van de ouders of grootouders. In Amsterdam, blijkt een analoog vaccinatieprogramma alleszins haalbaar, effectief en kosteneffectief te zijn.

Bij het opzetten van zulk een gevoelig doelgroepgericht programma moet men rekening houden met een mogelijke stigmatisatie. Andere ouders kunnen ook terugbetaalde vaccinatie vragen voor hun kinderen, als ze afreizen naar een hoog endemisch gebied. Anderzijds riskeren migrantenkinderen beschouwd te worden als verspreiders van "vreemde" ziekten in scholen.

De optie om alle Belgische zuigelingen te vaccineren heeft als voordeel dat er geen gevoelige ethische en equity-gerelateerde problemen zijn waarmee rekening dient te worden gehouden.

Deze optie is effectiever op lange termijn (deze optie wordt meer effectief dan doelgroepvaccinatie om reisgerelateerde import tegen te gaan na ongeveer 8 jaar). De combinatie van doelgroepvaccinatie van migrantenkinderen onder de 12 jaar (het eerste jaar) en universele zuigelingvaccinatie op de leeftijd van 1 jaar is echter de meest effectieve optie. Beide programma's zijn echter niet kosteneffectief.

Los van overwegingen ivm kosteneffectiviteit heeft universele zuigelingenvaccinatie tegen hepatitis A ook als risico dat het dient ingepast in een reeds overdrukke vaccinatiekalender, rond hetzelfde tijdstip als het Mazelen-Bof-Rubella vaccin, wat het bestaande vaccinatieschema in gevaar dreigt te brengen. Het is duidelijk dat het toevoegen van het anti-HAV vaccin niet kan verdedigd worden indien dit zou resulteren in een lagere deelname aan de vaccinatie voor Mazelen-Bof-Rubella of andere belangrijke vaccinaties voor kinderen.

AANBEVELINGEN

- Hepatitis A vaccinatie van de volledige bevolking kan niet aanbevolen worden gebaseerd op kosteneffectiviteit.
- Universele zuigelingenvaccinatie op de leeftijd van 1 jaar is niet kosteneffectief in België.
- Overheidsfinanciering van hepatitis A vaccinatie is aanbevolen bij kinderen van 1 tot 12 jaar die op reis gaan naar gebieden die hoog-endemisch zijn voor hepatitis A. Deze doelgroep zou de eerste en tweede generatie kinderen van 1 tot 12 jaar moeten omvatten wiens ouders of grootouders migreerden naar België vanuit een land dat hoog-endemisch is voor hepatitis A, alsook andere kinderen die reizen naar landen waar hepatitis A hoog-endemisch is.
- Blijvende aandacht is nodig voor sanitaire condities in scholen en kindercrèches, en hygiënische voorzorgen bij bewerkers van voedsel om zo de verspreiding te remmen van hepatitis A en andere infecties met feco-orale overdracht.

Scientific Summary

TABLE OF CONTENTS

SCIENTIFIC SUMMARY ..... **I**
LIST OF ABBREVIATIONS **2**
1 BACKGROUND AND LITERATURE REVIEW **4**
1.1 GENERAL BACKGROUND 4
1.2 CURRENT AVAILABLE HEPATITIS A VACCINES 4
1.2.1 Vaccine Tolerability 5
1.2.2 Vaccine Immunogenicity and Protective Efficacy 5
1.2.3 Early protection and duration of protection 7
1.2.4 Field effectiveness of routine vaccination programs 8
1.2.5 Field effectiveness of post-exposure administration and in outbreak control situation 9
1.3 ECONOMIC ANALYSES RELATED TO HEPATITIS A 9
1.3.1 Economic evaluations of hepatitis A vaccination options 10
1.3.2 Cost analyses of HAV outbreaks 14
2 DATA COLLECTION AND PREPARATIVE DATA ANALYSES **18**
2.1 HEPATITIS A VACCINATION IN BELGIUM 18
2.1.1 History of hepatitis A vaccine use in Belgium 18
2.1.2 Hepatitis A vaccine sales in Belgium 18
2.2 EPIDEMIOLOGY AND BURDEN OF HEPATITIS A IN BELGIUM 23
2.2.1 Incidence of reported lab confirmed hepatitis A cases in Belgium 23
2.2.2 Overview of recent outbreaks of HAV in the provinces of Antwerp, Limburg , West-Flanders, East-Flanders and Flemish Brabant 25
2.2.3 Seroprevalence 30
2.2.4 Hospitalization data (MKG/RCM) 33
2.2.5 A prospective survey of Non-hospital costs, Health Related Quality of life (HRQOL) impact and work loss related to Hepatitis A 55
2.2.6 Deaths attributable to Hepatitis A in Belgium 62
2.2.7 Liver transplantations attributable to hepatitis A 67
2.3 PARAMETER MEAN VALUES AND THEIR DISTRIBUTIONS FOR THE SIMULATIONS 72
3 METHODS **78**
3.1 GENERAL 78
3.1.1 Mathematical model structures 78
3.1.2 Model development 81
4 RESULTS **92**
4.1 DISEASE BURDEN 92
4.2 INCREMENTAL EFFECTIVENESS ESTIMATES 93
4.3 INCREMENTAL COST-EFFECTIVENESS ESTIMATES 98
4.3.1 Options with a general population impact 98
4.3.2 Targeted options with an impact in risk groups only 106
5 APPENDICES **117**
APPENDIX A **117**
SURVEYS DEVELOPED FOR REPORTED SYMPTOMATIC HEPATITIS A CASES 117
VRAGENLIJST B1 119
QUESTIONNAIRE B1 122
APPENDIX B **125**
ECONOMIC EVALUATIONS OF HEPATITIS A VACCINATION PROGRAM OPTIONS 125
APPENDIX C **145**
LIST OF HOSPITAL DIAGNOSES APPEARING WITH 'HEPATITIS A IN SECONDARY DIAGNOSIS' 145
APPENDIX D **149**
REGIONS AND AREACODES 149
6 REFERENCES **151**

LIST OF ABBREVIATIONS

CSS:	Conseil Supérieur de la Santé
CBA:	Cost-Benefit Analysis (KBA: Kosten-Baten Analyse)
CEA:	Cost-Effectiveness Analysis (KEA: Kosten-Effectiviteits Analyse)
CFR:	Case-Fatality Ratio
CLB:	Centra voor Leerlingenbegeleiding (School Health Centres)
COI:	Cost-of-illness
CPI:	Consumer Price Index
CUA:	Cost-Utility Analysis (KUA: Kosten-Utiliteits Analyse)
CUR:	Cost-Utility Ratio
DALY:	Disability Adjusted Life-Year
DTP:	Diphtheria Tetanus Pertussis
EPI:	Expanded Programme on Immunisation
FOD :	Fund for Occupational Disease / Federale OverheidsDienst
FOI:	Force of Infection
GP:	General Practitioner
HA:	Hepatitis A
HAV:	Hepatitis A Virus
HIV:	Human Immunodeficiency Virus
HBV:	Hepatitis B Virus
HCC:	Hepatocellular Carcinoma
HCW:	Health Care Worker
HGR:	Hoge Gezondheidsraad
IDU:	Injecting Drug Users
ICER:	Incremental Cost Effectiveness Ratio
IG:	Immuno Globulin
LOS:	Length Of Stay
LY:	Life Year
MMR:	Measles Mumps Rubella
MMRV:	Measles Mumps Rubella Varicella
PPP:	Purchasing Power Parities
QALY:	Quality Adjusted Life-Year
ROI:	Return on Investment
SHC :	Superior Health Council
SIPH:	Scientific Institute of Public Health (Wetenschappelijk Instituut Volksgezondheid (WIV))
SIR:	Susceptible-Infected-Recovered
TTO:	Time Trade Off
UK:	United Kingdom

USA:	United States of America
VAAE:	Vaccine Associated Adverse Events
VZV:	Varicella-Zoster Virus
WAIFW:	Who Acquires Infection From Whom
WHO:	World Health Organization
WIV:	Wetenschappelijk Instituut voor de Volksgezondheid
WTP:	Willingness To Pay
ELTR:	European Liver Transplant Registry

1 BACKGROUND AND LITERATURE REVIEW

1.1 GENERAL BACKGROUND

Hepatitis A is one of the most common vaccine-preventable infectious diseases causing significant morbidity and mortality, with annually an estimated 1.5 million documented cases worldwide. [1]

While no effective treatment is available against hepatitis A infection (other than liver transplantation for rare fulminant cases), vaccination of individuals implemented for more than ten years according to selected strategies at international and national levels, together with improved sanitary conditions, have contributed to a substantial reduction of the economic burden associated with disease management.

1.2 CURRENT AVAILABLE HEPATITIS A VACCINES

Several inactivated and live attenuated vaccines against hepatitis A were developed in the 1980s and licensed for use in the early 1990s. These vaccines are safe and well-tolerated, they are highly immunogenic, and they provide long-lasting protection against hepatitis A disease in children and adults. Four formalin-inactivated cell-culture produced whole-virus vaccines are available internationally: Havrix (HM 175 strain, GlaxoSmithKline Biologicals, Rixensart, Belgium)[2, 3] , Vaqta (CR326F strain, Merck & Co.,West Point, PA, USA)[4-6], Epaxal (RG SB strain, Berna Biotech Ltd, Bern, Switzerland)[7-9] and Avaxim (GBM strain, Sanofi Pasteur, Lyon, France)[10, 11] have been approved for use in most parts of the world, and Havrix and Vaqta are also licensed in the US.

Other hepatitis A vaccines are produced with limited distribution. These include a Chinese live attenuated vaccine (H2 strain, Zhejiang Academy of Medical Sciences, Hangzhou, People's Republic of China)[12], a vaccine manufactured by Vaccine and Bio-product Company 1 in Vietnam since 2004[13]; and Nothav, an inactivated vaccine manufactured by Chiron Behring GmbH and distributed in Italy only[14].

Several types of combination vaccines containing an inactivated hepatitis A vaccine have been developed in order to protect individuals against more than one infectious disease. Such (mainly travel-oriented) vaccines include Twinrix[15] (GlaxoSmithKline Biologicals, Rixensart, Belgium), the only combined vaccine against both hepatitis A and hepatitis B infections (licensed since 1996); other combined vaccines include Hepatyrix[16] (GlaxoSmithKline Biologicals, Rixensart, Belgium) and Viatim[10] (Sanofi Pasteur, Lyon, France), both protecting against hepatitis A and typhoid fever.

Inactivated hepatitis A vaccines all contain hepatitis A virus (HAV) antigen, but the content per vaccine dose is expressed in different units by manufacturers (**Table 1**). Recommended vaccination schedules, ages for which the vaccine is licensed, and whether there is a pediatric and adult formulation also vary. All vaccines are licensed from one year of age in most countries, including the United States since September 2005[17, 18], except in Australia[19, 20] where vaccines are licensed from two years, and in China where Epaxal is licensed from 6 months on. The inactivated vaccines are produced according to similar manufacturing processes involving whole-virus preparations of HAV strains growing in human MRC-5 diploid cell cultures, with subsequent virus purification and inactivation with formaldehyde. Havrix (HM 175 strain), Vaqta (CR326F strain) and Avaxim (GBM strain) are adjuvanted with alum while Epaxal (RG SB strain) contains a liposome adjuvant in the form of immunopotentiating reconstituted influenza virosomes (IRIV). Havrix and Avaxim contain 2-phenoxyethanol as a preservative, while the other vaccines are preservative-free formulations[3, 4, 7, 11]. All vaccines are administered via intramuscular injection, according to varying dosages and schedules, as described in Table 1.

Table 1: Dosage and schedule for inactivated monovalent hepatitis A vaccines (in alphabetical order)TTTT

Vaccine	Antigen content (HAV strain)	Volume (ml)	2-dose schedule (months)
Avaxim® 80U Pediatric	80 antigen units (GBM)	0.5	0, 6-12
Avaxim ®160U	160 antigen units (GBM)	0.5	0, 6-12
Epaxal® Junior	12 IU (RG SB)	0.25	0, 6-12
Epaxal®	24 IU (RG SB)	0.5	0, 6-12
Havrix™720 Junior	720 El.U (HM 175)	0.5	0, 6-12
Havrix™1440 Adult	1440 El.U (HM 175)	1	0, 6-12
Vaqta®	25 U (CR326 F)	0.5	0, 6-18
Vaqta®	50 U (CR326 F)	1	0, 6-18

If medically indicated, such as in hemophiliacs or in patients under anticoagulation, all four vaccines can be given subcutaneously [21-24].

1.2.1 Vaccine Tolerability

To date, several million doses of hepatitis A vaccines have been administered to children and adults worldwide, with no serious adverse event statistically linked to their use yet[25]. The safety profile of inactivated hepatitis A vaccines has been extensively reviewed and results from clinical trials, as well as post-marketing surveillance studies, have demonstrated that the vaccines are all safe and well-tolerated[3, 26-28]. The most commonly reported adverse events have included mild and transient local site reactions, such as pain, swelling and redness (21% in children and 52% in adults); Epaxal has a two to three times lower rate of local reactions in comparison to alum-adsorbed hepatitis A vaccines[28, 29]. General reactions such as fever, fatigue, diarrhea, vomiting and headache were reported in less than 5% subjects[20, 30].

1.2.2 Vaccine Immunogenicity and Protective Efficacy

The absolute minimum level of anti-HAV antibodies required to prevent HAV infection has not been defined. Experimental studies in chimpanzees have shown that low levels of passively transferred antibody (<10 mIU/mL) obtained from vaccinated persons do not protect against infection but do prevent clinical hepatitis and virus shedding[31].

In the absence of absolute lower protective level of antibody required to prevent HAV infection, the lower limit of detection of the specific assay used in a study is generally considered as an accepted correlate of protection, i.e. 20 or 33 mIU/ml by ELISA in clinical studies with Havrix; 20mIU/ml by ELISA with Avaxim and Epaxal, and 10mIU/ml by ELISA for Vaqta[3, 5, 7, 10].

Currently licensed inactivated hepatitis A vaccines have proven highly immunogenic in extensive clinical studies, conferring protective immunity against the disease two to four weeks after first dose administration. Recent data have shown that a vast majority of individuals seroconvert within two to four weeks of vaccination, with rates ranging from 95% to 100% in children and adults. Administration of the second dose of the primary schedule (6 to 18 months after the first dose) ensures long-term protection[8, 32]. Review of the immunogenicity data for each vaccine as well as results from several comparative clinical trials demonstrate the equally high immunogenicity and interchangeability of hepatitis A vaccines[2, 10, 28, 33].

The protective efficacy of inactivated hepatitis A vaccines against clinical disease has been documented in several controlled clinical efficacy trials. The cumulative protective efficacy of the vaccination course with Havrix in more than 40,000 Thai children aged 1-16 years was 95%[34].

The observed protective efficacy of Vaqta was 100% after one vaccine dose in a trial involving more than 1000 children aged 2-16 years from a highly endemic community in the United States[4]. In a recent trial involving 274 Nicaraguan children aged 1.5-6 years, the protective efficacy of a single dose of Epaxal was also 100%[35].

The presence of passively transferred antibodies from previous maternal HAV infection has been shown to result in reduced antibody response to hepatitis A vaccination in infants[36-38]. However, in spite of lower antibody concentrations observed after primary vaccination of infants born to anti-HAV seropositive mothers, several studies have indicated that priming and immune memory were induced, as demonstrated by the anamnestic response at the time of booster[36-42]. This was the case after a second vaccine dose administered at 12 months to 300 infants either born to anti-HAV seronegative or seropositive mothers in a study conducted in Israel[39]. Similarly, in a study conducted in Turkey with children who had received primary vaccination at 2, 4 and 6 months of age, all subjects showed anamnestic response after booster vaccination at 4 years of age[40]. At 15 months of age, protective levels of antibody were also present in 93% of American Indian infants born to anti-HAV positive mothers, who had received primary immunization at 2, 4 and 6 months or at 8 and 10 months of age[36]. Effective hepatitis A vaccination was also demonstrated in a study with 30 infants aged 6-7 months –half of them with maternal antibodies- and 30 children aged 6-7 years who were all seroprotected at Month 1 and Month 12 post-vaccination and additionally showed a strong antibody response to booster vaccination[42].

Such findings relating to hepatitis A vaccine immunogenicity in children younger than two years of age, as well as studies which have shown that hepatitis A vaccine may be effectively and safely co-administered with other pediatric vaccines, such as diphtheria-tetanus-acellular pertussis, inactivated and oral polio, *Haemophilus influenzae* tybe b vaccine and hepatitis B vaccines[37, 38] are of particular importance in the implementation of prevention strategies involving routine childhood vaccination programs. Other studies in adults have demonstrated effective and safe co-administration of hepatitis A vaccine with traveler vaccines, including hepatitis B, polio, diphtheria, tetanus, typhoid fever, yellow fever, rabies, cholera, and Japanese encephalitis[43-46].

In spite of an initially slower immune response observed in subjects over 40 years following administration of hepatitis A vaccines, response rates were similar to those observed in younger individuals on completion of full vaccination course[47, 48]. These data are confirmed by anti-HAV seroconversion rates of at least 98% in retrospective analyses of subjects ≥40 years who received a combined vaccine against hepatitis A and B[49, 50].

Other conditions which may result in a lower immune response to hepatitis A vaccination include HIV infection and chronic liver disease. Limited data reported from studies conducted with HIV-infected male individuals have indicated that they had lower antibody concentrations than HIV-negative individuals and that approximately 75% had protective antibody levels on completion of vaccination course[20]. Results from several trials evaluating the safety and immunogenicity of hepatitis A vaccine in chronic liver disease patients in the United States, Europe and Asia, including data collected in children, have been extensively reviewed and discussed elsewhere[3, 20]. Mainly, these data indicate that hepatitis A vaccine was generally well-tolerated and that the proportions of subjects with protective antibody levels were similar to those obtained in healthy individuals on completion of vaccination course while final antibody concentrations were substantially lower.

A few studies in transplant recipients also indicate a lower immune response following hepatitis A vaccination. While one study reported an acceptable 97% seropositivity in vaccinated liver transplant patients after two doses of hepatitis A vaccine on a 0-6 month schedule, as compared to 100% in the control group, a third group of renal transplant recipients showed only 72% seropositivity. Moreover, seropositivity after the first dose was obtained in only 41% of liver transplant patients and 24% of renal transplant patients, compared to 90% in the control group. Therefore, the authors concluded that transplant recipients should receive a full vaccination course before a potential exposure to hepatitis

A virus[51]. Two years later, only 59% and 26% of the seroconverters maintained anti-HAV seropositivity in the groups of liver transplant and renal transplant patients, respectively. The rate of antibody loss in transplant patients therefore seems substantially higher[52]

Another study in liver transplant patients reached only 26% seropositivity after a full hepatitis A vaccination schedule[53]. These data reveal a lower hepatitis A vaccine efficacy in transplant patients, especially in those with stronger immunosuppressive regimens.

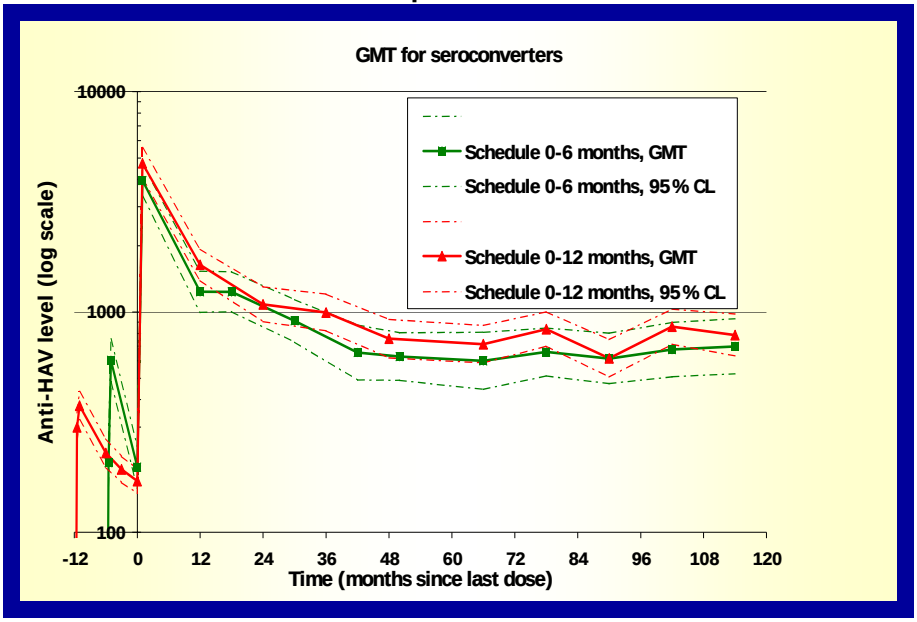
Hepatitis A vaccine has a recommended 2-dose schedule, with the second dose being administered at 6-12 months in the case of Havrix, Avaxim and Epaxal, and at 6-18 months in the case of Vaqta. However, timing of the second dose is flexible since an anamnestic response has been shown to be triggered by a second dose when administered several years after the first vaccine dose in children and adults[53-57]. Flexible 2-dose vaccination schedules with a "delayed" second dose are of critical importance due to the fact that travelers often miss the second dose and present themselves some years later with a new/repeated indication for hepatitis A vaccination. In addition, a flexible schedule might help introducing hepatitis A vaccines into established childhood routine vaccination programs. For example, a vaccination schedule for infants/children with the first dose administered during the second year of life and a second dose given at school entry at the age of 5-6 seems worth investigating. Also, additional long-term follow-up studies of individuals who have received a single vaccine dose should help formulate future recommendations in terms of dosing schedule.

1.2.3 Early protection and duration of protection

Hepatitis A vaccines confer early protection, as confirmed by recent data showing that a majority of individuals seroconvert within two weeks of vaccination, well within the 28-day incubation period of the virus. Travelers receiving the vaccine any time prior to departure may thus be expected to be protected against the disease[8, 10, 32].

With regards to duration of immunity, long-term follow-up studies have shown persistence of protective anti-HAV antibodies for at least 5 years in children and up to more than 12 years in adults, post-vaccination[9, 41, 58-60]. The kinetics of antibody persistence 10 years after primary immunization of 313 seronegative healthy adults with a 2-dose inactivated hepatitis A vaccine administered either on a 0-6 or 0-12 schedule is presented in **Figure 1**[61].

Figure 1:Anti-HAV geometric mean titer (GMT) for the 0-6 and the 0-12 month schedules within their respective 95% confidence intervals



A robust immune response was also demonstrated in 31 vaccinated adults challenged with a pediatric dose of hepatitis A vaccine antigen 12 years post-primary vaccination, while geometric mean anti-HAV antibody concentration was ≥15 IU/L before booster administration[61].

Mathematical models using data from vaccinated adults have estimated protective antibodies to persist for at least 25 years in more than 95% of vaccinees[9, 10, 62].

The role of immune memory in conferring protection for individuals vaccinated against hepatitis A was reviewed in 2002 by an International Consensus Group on HAV Immunity[63]. The group concluded that evidence is accumulating that hepatitis A vaccines elicit immune memory persisting even after loss of detectable antibody. It recommended that reliance be placed on immune memory rather than booster doses to protect healthy individuals who received a full vaccination course. Based on demonstrated persistence of protective antibodies for more than 10 years post-vaccination, their estimated mathematical persistence for more than 25 years post-vaccination, and the presence of immune memory considered to confer protection even beyond detectable circulating antibodies, hepatitis A booster vaccination has been considered to be unnecessary in the healthy individual. Additional long-term follow-up studies should validate this expert consensus.

1.2.4 Field effectiveness of routine vaccination programs

Hepatitis A routine immunization of young children has proven effective in rapidly reducing disease incidence, and maintaining very low incidence levels among vaccine recipients as well as across all other age groups, thus demonstrating the development of herd immunity, in a number of settings. In the United States, the introduction of immunization programs for children, with a primary focus on pre-school children (i.e. 2-5 years), living in communities with the highest incidence rates, has shown a decrease in disease incidence similar to rates in the national average or even lower. In 2003, the overall incidence rate of hepatitis A disease in the United States was 2.6 per 100 000, representing an overall decline of 76%,

while targeted states had a reduction of 88%- even with levels of vaccination coverage not exceeding 50%- and 53% decrease was observed in non-targeted states[64-66].

A national toddler immunization program in place in Israel since 1999 has also demonstrated vaccine effectiveness, with a decrease of annual incidence rate of hepatitis A disease from 50.4 per 100 000 (1993-1998) to 2.2-2.5 per 100 000 (2002-2004), representing more than a 95% reduction. This marked decline was seen in targeted vaccine recipients (85-90% coverage), as well as in all other age groups, thus demonstrating the effectiveness of hepatitis A vaccination, as well as the development of herd immunity[67]. Mass vaccination programs also proved effective in localized regions of intermediate to high HAV endemicity of industrialized nations with otherwise low endemicity levels, such as the Puglia region of Italy, the Catalonia region of Spain, and in North Queensland, Australia[19, 68-70].

The real impact and added value of such mass vaccination programs will need to be confirmed by continued disease surveillance. Indeed, although vaccination was a major contribution to the marked declines observed in the incidence of hepatitis A disease in Israel and the United States, it is difficult to evaluate to what extent this reduction could be partly due to improved sanitation and hygiene or to the epidemic cycles that characterized the hepatitis A virus in the past[64, 67, 71]. Furthermore, the long term effects of herd immunity are yet to be observed. As widespread vaccination continues, the accumulation of susceptibles (in unvaccinated (age) groups) due to reductions in natural exposure may in the long run, for instance, influence the frequency and size of outbreaks (outbreaks were observed to become less frequent and smaller in size in the short run in some settings (e.g. see Hanna et al[19]). The associated increase in the average age at infection may also increase the occurrence of severe and fatal hepatitis A in adults and the elderly. These long term effects ultimately depend on vaccine uptake, the duration of vaccine induced protection (and therefore the realization of expectations regarding immunological memory), and concomitant improvements in safe water and sanitation in specific settings.

1.2.5 Field effectiveness of post-exposure administration and in outbreak control situation

Studies in chimpanzees[72], further supported by randomized trials in humans[73, 74], have shown that hepatitis A vaccine is effective in preventing HAV infection when administered post-exposure. Although the post-exposure window for successful vaccination is yet to be defined, there is increasing evidence of the efficacy of hepatitis A as a valid alternative to passive post-exposure prophylaxis with immune globulin, allowing, in particular, for a better control of outbreak situations.

Results from studies conducted in chimpanzees have also shown that vaccinated animals did not shed hepatitis A virus once exposed to the wild-type virus, thus demonstrating that the use of vaccines is effective to control spread in outbreaks[31].

The effectiveness of hepatitis A vaccination to control outbreak situations has been reported in various settings in the United States, including rural communities from Alaska, and Europe, including Slovakia, Croatia, the UK and Italy[2, 20]. Recent data have reported the successful use of hepatitis A vaccine to control an outbreak among intravenous drug users in Bristol, UK in 2000 [75] while the duration of two outbreaks was also substantially shortened in a maternal school and a day care centre in Tuscany, Italy, at the end of 2002[76].

1.3 ECONOMIC ANALYSES RELATED TO HEPATITIS A

We reviewed cost studies of hepatitis A outbreaks, as well as economic evaluations of hepatitis A vaccination strategies. Especially for the latter we were able to build on the recent review by Anonychuk et al [77], who made a synthesis of the literature on the cost-effectiveness of hepatitis A vaccination. Anonychuk et al's review was - to a minor extent - limited in three ways. First, Anonychuk et al. only review articles on the cost-effectiveness of vaccination against hepatitis A until September 2006. Second, cost-benefit analyses were excluded from their search. Third, studies dealing only with cost aspects of HAV outbreaks were not reviewed by Anonychuk et al[77]

On 04/10/07 the broad search terms "cost* AND hepatitis A" were used to extract publications from Pubmed, resulting in 2721 hits. From this list we selected only articles published in 2006 or later, resulting in 306 results. The same search in Current Contents resulted in 321 publications from 2006 onwards. A consultation of Econlit did not yield additional publications.

On April 28, 2008 we extended our search for articles on the cost of HAV-outbreaks. We performed the following search in Pubmed, NHSEED, EconLit and DARE: (cost* OR economic) AND outbreak* AND "hepatitis A". The search in PUBMED resulted in 76 different publications, whereas in web of science, NHSEED and DARE we respectively found 102, 11 and 0 articles. After elimination of duplicates and inspection of all abstracts, 22 full-text articles were retrieved.

The search terms "cost-benefit AND hepatitis A", "benefit-cost AND hepatitis A", and "benefits AND costs AND hepatitis A" were used in Pubmed resulting in 957 hits. After controlling for duplicates and checking titles on usefulness only 17 results remained. When all results of previous searches were united and checked for duplicates, only 605 results were left. Of these, only 90 were considered useful. In the bibliographies of other articles we found another 8 new articles. The final list consisted of 102 articles. Most of these were not reviewed by Anonychuk et al but in the search for costs of outbreaks there were some overlapping articles. On the basis of the abstracts, we made the following distinctions:

- Studies without any form of economic analysis: 34
- Articles without full economic evaluation (i.e. analysing costs and effects of more than 1 option), or without cost analysis of an outbreak situation : 33
- Cost-effectiveness or cost-utility analyses already reviewed by Anonychuk et al: 9
- Cost-effectiveness or cost-utility analysis not-reviewed by Anonychuk et al: 7 articles

- Cost-benefit studies: 8 articles
- Cost analyses of an outbreak: 22 articles

General characteristics of studies related to the latter 4 groups are shown in **tables 2, 3, 4, 5 and 6** below. Detailed references and summaries for the studies retrieved can be found in appendix B.

1.3.1 Economic evaluations of hepatitis A vaccination options

Table 2 presents an overview of economic evaluations on hepatitis A vaccination, by vaccination strategy, population and intervention.

First, All available studies are categorised under three vaccination options: universal, targeted and "other" (screening for antibodies and vaccination of susceptibles). Universal vaccination has the highest proportion of ICER's < $20,000 (55%) and seems to be the most favourable strategy. Especially universal vaccination of infants appears to be economically attractive with 67% of ICER's below $20,000 per QALY or LY.

Universal vaccination of adults produced ICER's all higher than $100,000 and seems to be less worthwhile. CEA's, which expressed the results as costs per case prevented, show for universal vaccination a median of $5,335 while the median for targeted and susceptibles-only was respectively $18,258 and $19,033 per case prevented. For areas with higher incidence rates like Chile, Spain and high incidence states in the USA, universal vaccination was found to be cost saving.

Note however, that many of these results focus on the costs per (QA)LY gained of vaccination versus doing nothing. The correct approach for decision making would be to evaluate universal versus targeted vaccination, or current practice. It is equally noteworthy that many of these studies adjust the incidence of reported cases by a significant age-independent factor (which is often poorly substantiated), to account for atypical or simply unreported clinical cases. In the absence of seroprevalence data in accordance to which to fit such underreporting factors, they will remain highly uncertain.

Targeted vaccination had an ICER of less than $20,000 in 43% of the reviewed studies. The most attractive median costs per case prevented were for targeted vaccination of specific risk groups ("other" such as patients with chronic HCV, prison inmates, restaurant workers, etc.): $2,303, military personnel in high endemic areas: $16,332, and travellers: $26,046. For targeted vaccination of health care workers most ICER's were above $100,000. Options identifying first susceptible individuals through blood screening, and vaccinating only those that are susceptible, were usually found to be unattractive, except for risk groups with a high risk exposure, especially in high incidence regions.

Second all reviewed studies are grouped by vaccinated population. Sixty-seven percent of studies on infants and 50% of studies on children and adolescents produced ICER's below $20,000.

Grouping studies by the vaccine that was used indicates that all studies with the combined HAV/HBV vaccine had ratios of less than $100,000 per (QA)LY gained. The monovalent HAV vaccine produced the same result only in 65% of the studies reviewed. In countries where the combined HAV/HBV vaccine can replace the monovalent hepatitis B vaccine, the attractive incremental cost-effectiveness seems intuitively logical, as the incremental vaccination costs can be minimised through attractive pricing strategies of the producer and the redundancy for administration costs. However, in many countries, including Belgium, hepatitis B vaccine is included in the universal infant vaccination strategies as part of a penta or heptavalent combination vaccine DTP-Hib-IPV-HBV. In these countries the combined HBV/HAV vaccine is marketed as a travel vaccine. The risks to travellers of hepatitis B is however very specific.

Table 3 categorises all CEA's according to study characteristics. Industry funded studies had an ICER of less than $20,000 in 60 % of the CEA's while this was only 6 % if there was non-industry funding. Other characteristics that are related to favourable ICER's are the inclusion of work loss costs and adjustments for under-reporting (note however, the remarks related to underreporting above). Incidence (or risk exposure), vaccination cost and discount rate were often shown to be the most influential parameters in sensitivity analyses.

Table 2: Summary of Cost-effectiveness of Hepatitis A Vaccine, by Vaccination Strategies, Population and Intervention

	Cost per LY or QALY					Cost per case prevented		
Study characteristics	**Total No. Studies**	**Total No. Comparisons**	**< $20,000 n(%)**	**$20,000-$100,000 n(%)**	**>$100,000 n(%)**	**Total No. Studies**	**Total No. Comparisons**	**Median**
Vaccination Strategy								
Universal	13	61	34 (55)	13 (21)	14 (23)	6	13	$5,335
Infant	7	36	24 (67)	8 (22)	4 (11) *	3	4	$390
Children/pre/adolescent	5	22	11 (50)	5 (23)	6 (27) †	3	7	$5,335
Adults	2	4	0 (0)	0 (0)	4 (100)	1	2	$297,485
Targeted	8	21	9 (43)	4 (19)	8 (38)	9	23	$18,258
Travelers						3	6	$26,046
Health care workers	3	9	1 (11)	2 (22)	6 (67)	2	3	$129,757
Military						2	6	$16,332
Other high risk***	5	12	8 (67)	2 (17)	2 (17)	3	8	$2,303
Other**	6	18	2 (11)	9 (50)	7 (39)	7	17	$19,033
Travelers						3	4	$23,555
Health care workers	2	8	0 (0)	4 (50)	4 (50)	2	3	$133,591
Patients with chronic HCV	2	8	1 (13)	5 (63)	2 (25)	1	1	$479,024
Adults/General population	1	1	0 (0)	0 (0)	1 (100)	2	6	$5,227
Other groupsΦ	1	1	1 (100)	0 (0)	0 (0)	1	2	$6,672
Population								
Infants	7	37	25 (67)	8 (22)	4 (11) *	3	4	$390
Children/pre/adolescent	5	22	11 (50)	5 (23) $\Phi\Phi$	6 (27) †	3	9	$5,832
Travelers						3	10	$25,836
Health care workers	3	17	1 (6)	6 (35)	10 (59)	2	6	$131,674
Adults/General population	3	7	2 (29)	0 (0)	5 (71)	3	12	$6,653
Patients with chronic HCV	2	10	1 (10)	5 (50)	4 (40)	1	1	$479,024
Military (all case prevented)						2	7	$11,474
Other high risk***	3	7	5 (71)	2 (29)	0 (0)	1	5	$0
Intervention								
HA vaccine	15	79	31 (38)	20(25)	28(35)	12	37	$10,271
HA/HB vaccine	10	15	9(60)	6(40)	0(0)	1	2	$0
Immunoglobulin						6	15	$26,979

Table 3: Summary of Cost-effectiveness of Hepatitis A Vaccine, by Study Characteristic and Methodological Factors (for further details, see appendix B)

	Cost per Life year of QALY gained					Cost per case prevented		
Study characteristics	**Total No. Studies**	**Total No. Comparisons**	**<$20,000 n(%)**	**$20,000-$100,000 n(%)**	**>$100,000 n(%)**	**Total No. Studies**	**Total No. Comparisons**	**Median**
Year of publication								
1990-1995						4	16	$25,836
1996-2000	5	14	7	2	5	5	28	$6,456
2001-2007	17	86	38	24	24	4	10	$390
Location								
US	13	48	21	14	13	1	2	$390
Canada	3	20	6	6	8			
Europe	1	1	1	0	0	11	51	$13,344
Other	5	31	16	7	8	1	1	$479,024
Funding								
Industry	13	55	34	11	10	3	12	$9,594
Non-industry	4	19	2	8	8	1	14	$5,584
Not reported	5	26	7	8	11	9	28	$26,769
Model Type								
Cohort	19	86	40	25	21	10	46	$9,595
Dynamic	3	13	4	2	8	1	2	$91,889
NR						2	6	$16,330
Work Loss Cost*								
Yes	17	51	29	11	11	7	19	$19,033
No	14	49	15	16	18	5	27	$5,335
Public Health Cost								
Yes	8	45	19	12	14	3	7	$19,033
No	13	55	25	15	15	10	47	$11,474

1.3.2 Cost analyses of HAV outbreaks

Despite the self limited non-malignant course hepatitis A usually takes, the economic impact of an HAV outbreak can be substantial. Nonetheless up till now, a fairly limited number of studies describing the economic impact of HAV outbreaks have been published.

Intuitively, the bulk of the economic burden of hepatitis A is often attributed to the indirect costs because people with symptomatic infection may be unable to work for several weeks, while the cost of treating them is considered only minor.[78], [79], [80]]However, the descriptions of the outbreaks we retrieved from the literature (**table 4**) show a different picture. The indirect costs represented 8% to 48% (average 26.8%, median 20%), whereas the direct costs made up 52% to 92% (average 76.8%, median 78%) of the total costs of the outbreaks. Note that, in view of the valuation method used, indirect cost estimates are sensitive to the employment status of the persons affected by the outbreak.

In Cost of Illness studies and economic evaluations of HAV vaccination the direct costs may typically be underestimated. The COI studies summarized in **table 5** estimated the direct cost per patient between $583 and $2,586. The economic evaluations in **table 6** we retrieved for the same geographic areas, also use estimates for direct costs per case that are, on average, smaller: ranging from $183 (for a non-hospitalized case) to $9,506. For instance for the US, two widely cited COI studies, estimate the direct costs of an adult hepatitis A case at $1,295 [81] and $2,586 [79]. To come to this estimate these studies applied a hospitalization rate of 15% and 14%, respectively. Cost-effectiveness analyses for adults and adolescents from the same country estimated the average direct cost per case at $985 ([82]) (with 10 % to 43 % of cases hospitalized) and $1,628 ([83]) (with 16% of cases hospitalized). However direct costs per case in the reviewed outbreaks in the US, which included the public health costs of outbreak control, were $29,809 [84]; $4,302 [85] and $1,991 [86]. The respective hospitalization rates were 5%, 6% and 18%. These cost estimates from outbreaks are on average higher than the ones obtained in COI studies or used in economic evaluations. This may imply that he average costs per case (especially for non-hospitalized cases) might be underestimated in economic analyses. In one outbreak massive post-exposure prophylaxis costed $250,881 per reported case. Disease control costs can be a substantial component of total costs, especially if the outbreak was related to a food handler.

Based on the published costing studies of outbreaks, it remains difficult to estimate a value that can serve as a general approximation for outbreak control costs for inclusion in economic analyses. Only a small proportion of outbreak control measures can be considered as fixed cost, e.g. the costs of school cleaning interventions or public notification campaigns. On this fixed part, little is documented in the articles we reviewed. The bulk of the control costs are variable (i.e. related to the size of the outbreak), dependent on the main source of the outbreak (foodhandler or not) and the control strategy that was chosen. Bauch et al [87] made the only published economic evaluation to include the costs for outbreak control and estimated these at $355 per case. This could represent a good estimate of disease control costs in school outbreaks, but if there is a food handler involved, these costs could be significantly higher. Control strategies with massive public notification can provoke panic and this can lead to an overconsumption of prophylaxis, as was the case in Denver. Implementing no outbreak control measures, as was the case in Puglia, can still turn out to be very costly.

Many authors of the studies under review emphasized the difficulties in gathering the required information. Outbreaks are often documented from an epidemiological point of view, but the collection of cost data remains very rare. For instance, on only one of 16 outbreaks that occurred in Canada between November 1998 and September 2004, information on the public cost of the incident was available.[88] Information on private medical consumption is even harder to retrieve.

The outbreaks described in the literature could be subject to publication bias since outbreaks with an exceptional impact may stimulate interest in economic analysis more than the "average outbreak". In the outbreaks described here, local economies had to face a cost ranging from $140,000 to $36 million over a short time span. The COI estimates in the outbreak studies seem to be higher than estimates produced for sporadic cases. Post exposure prophylaxis is a major cost factor, especially for food borne outbreaks. Economic evaluations (eg, cost-effectiveness analyses) often ignore these costs. If the epidemiological situation, for which such an evaluation is designed, makes it unlikely for an outbreak to occur, or if it is likely that outbreaks remain very small (and non-food borne), then the exclusion of outbreak-specific costs may remain an acceptable analytical choice.

Table 4: Summary of studies on the cost of an outbreak of hepatitis A

Location	Denver, US [84]	Spokane, US [85]	Franklin County, US [89]	Narzole, Italy [90]	Puglia, Italy [91]	Liverpool, UK [92]	Toronto, CND [88]
Main source of outbreak	Food handler	Injecting drug use	Men who have sex with men	Primary School or day care centre children	Infected food and person to person	Primary school children	Food handler
Nr of cases	43	590	136	11	5889	9	3
Direct costs	$1,281,800 ($29,809 ; 92%)	$2,538,004 ($4,301 ; 78%)	$270,720 ($1,991 ; 52%)	$118,499 ($10,773 ; 84%)	$28,398,494 ($4,822 ; 78%)	NS	NS
Direct treatment costs	$80,292 ($1,867 ; 6%)	$1,148,025 ($1,946 ; 35%)	$220,615 ($1,622 ; 42%)	$116,876 ($10,652 ; 83%)	$28,398,494 ($4,822 ; 78%)	NS	NS
Non-hospital costs	$54,195 ($1,260 ; 4%)	$445,760 ($756 ; 14%	$78,410 ($577 ; 15%)	$11,853 ($1,078 ; 8%)	$4,411,325 ($749 ; 12%)	NS	NS
Hospital costs	$26,097 ($607; 2%)	$702,265 ($1,190 ; 21%)	$140,527 ($1,033 ; 27%)	$105,024 ($9,548 ; 75%)	$23,987,169 ($4,073 ; 66%)	NS	NS
Direct control costs	$1,201,508 ($27,942 ; 87%)	$1,389,978 ($2,356 ; 42%)	$50,105 ($368 ; 10%)	$1,622 ($147 ; 1%)	NA	$7,818 ($869)	$601,440 ($200,480)
Prophylaxis used	IG	IG	IG	IG	NO	Vaccine	Vaccine & IG
Tests	$232,205 ($5,400 ; 17%)	NS	$381 ($3 ; 0%)	NS	NA	NS	NS
Prophylaxis costs	$785,064 ($18,257 ; 57%)	$1,389,978 ($2,356 ; 42%)	$22,290 ($164 ; 4%)	$318 ($29 ; 0%)	NA	$5,478 ($609)	$342,019 ($114,006)
Health personnel costs	$184,239 ($4,285 ; 13%)	NS	$27,434 ($202 ; 5%)	$1,304 ($119 ; 1%)	NA	$1,302 ($145)	$259,421 ($86,474)
other	NS	NS	NS	NS	NA	$1,036 ($115)	NS
Indirect costs	$106,653 ($2,480 ; 8%)	$733,533 ($1,243 ; 22%)	$249,318 ($1,833 ; 48%)	$21,923 ($1,993 ; 16%)	$7,892,334 ($1,340 ; 22%)	NS	NS
Productive time lost	$42,083 ($979 ; 3%)	$733,533 ($1,243 ; 22%)	$249,318 ($1,833 ; 48%)	$21,923 ($1,993 ; 16%)	$7,180,231 ($1,219 ; 20%)	NS	NS
Other time lost	$64,570 ($1,502 ; 5%)	NS	NS	NS	$712,102 ($121 ; 2%)	NS	NS
Mean Number of workdays lost	12.5*	9.1	12	7.5	12.8	NS	NS
Total cost	$1,388,452 ($32,290; 100%)	$3,271,537 ($5,545 ; 100%)	$520,039 ($3,824 ; 100%)	$140,422 ($12,766 ; 100%)	$36,290,828 ($6,162 ; 100%)	NS	NS

Table 5: cost-estimates for hepatitis A patients in miscellaneous studies on the cost of illness (in $US2007)

First author	Tolsma et al [80]	Chossegros et al[93]	Berge et al [79]	De Juanes et al [94]	Todd [78]	Diel et al [95]
Region/year	US	France	US	Spain	US	Germany
Direct costs per case	$583	$655	$2.586	NS	NS	$1.020
Indirect costs per case	$967	$1.988	$7.361	NS	NS	$4315 / $449([1])
Total cost	$1.550	$2.782	$9.948	$764	$9.691	$5336 / $292

Table 6: cost-estimates from CEA's for hepatitis A in the US, Canada and France (in $US 2007)

Author	Bauch et al. [87]	Jacobs et al.[96]	Myers et al.[97]	Péchevis et al[98]	Jacobs et al. [96]	O'connor et al [83]	Smith et al [99]
Population studied	Universal Canada	Adolescents US	Chronic HCV US	Sec. infect. France	Children US	Adults US	Students US
Outbreak control costs	$430	NS	No	NS	NS	NS	NS
Direct costs per case	From $1000 to $1686	$985	$3783 (moderate case)	$356 (mild) $3355 (hosp.)	$668 (nonhosp) $9506 (hosp)	$183 (nonhosp.) $9219 (hosp.)	NS
Cost per case	From $1607 to $3189	$2658	NS	NS	NS	NS	$10491

* Median instead of mean
IG: Immunoglobulin
NS: Not stated, NA: Not applicable

[1] For an adult/for a child

2 DATA COLLECTION AND PREPARATIVE DATA ANALYSES

2.1 HEPATITIS A VACCINATION IN BELGIUM

2.1.1 History of hepatitis A vaccine use in Belgium

Havrix came on the Belgian market in 1992. Originally, Havrix 720 was a vaccine for adults in a 3 dose schedule (0,1,6m), and Havrix 360 was given according to the same schedule to children. Havrix 360 was subsequently taken off the market and replaced by Havrix 720 ped in a 2 dose schedule (0,6m). Havrix 720 for adults was replaced by Havrix 1440 adults in a two dose schedule (0,6m).

Twinrix came on the market in 1996, with a pediatric and an adult formulation, both delivered in a 3 dose schedule (0,1,6m). Since 2001 Twinrix is offered free of charge by the Fund for Occupational Risks (Fonds voor de Beroepsziekten/ Fonds des Maladies Professionelles) to health care workers (HCWs) who are at increased risk of hepatitis B, in replacement of the monovalent hepatitis B vaccine these HCWs were given up till then. There was no scientific rationale for the switch from monovalent hepatitis B to bivalent hep A/hep B vaccine, other than that these HCWs could enjoy additional protection against hepatitis A for a small additional cost.

Epaxal came rather recently to market (2004), and has till now been a very marginal player on the market.

Table 7 shows the 2006 public price level for these vaccines in Belgium, indicating that the cost of a full schedule are roughly between €60 and €90, depending on formulation.

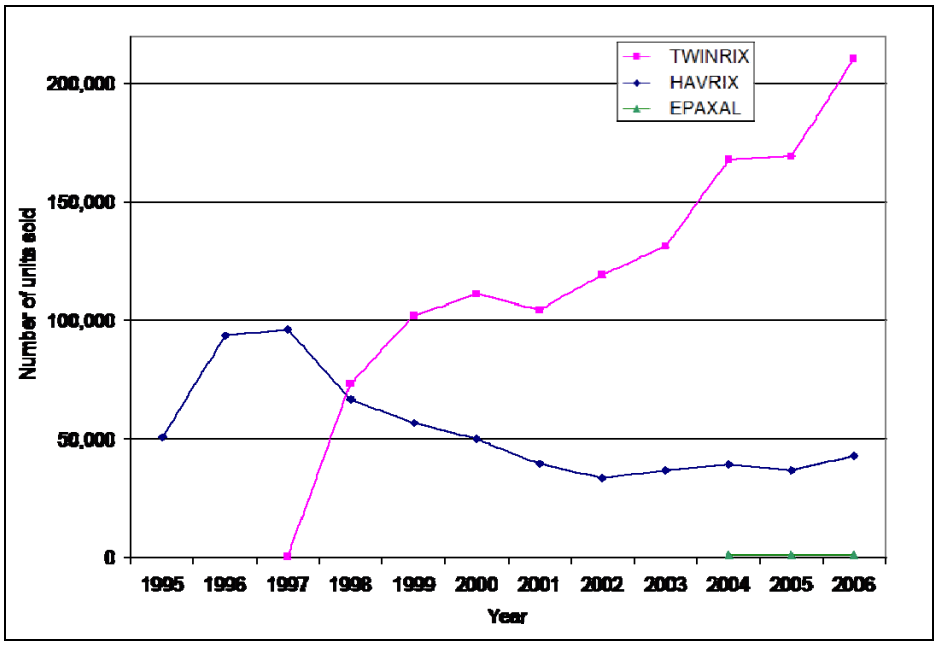
Table 7: Cost of hepatitis A vaccine in Belgium (2006)

Target	Brand	Cost/dose (Euros)	Cost/immunization (Euros)
Adults	Epaxal® (Docpharma)	39.58	79.16 (2 doses)
	Havrix® (GSK)	45.66	91.32 (2 doses)
	Twinrix® (GSK)	45.84	137.52 (3 doses)
Children (> 1 y)	Epaxal® (Docpharma)	39.58	79.16 (2 doses)
	Havrix® (GSK)	30.04	60.08 (2 doses)
	Twinrix® (GSK)	30.24	90.72 (3 doses)

2.1.2 Hepatitis A vaccine sales in Belgium

The IMS Health database was used to extract pharmacy-based sales figures of hepatitis A vaccines in Belgium. It shows that the bivalent hepatitis A – hepatitis B vaccine Twinrix is market leader by far, and has taken over this position from the monovalent hepatitis A vaccine Havrix since 1998.

Figure 2: Number of doses sold by year, for three main product groups of hepatitis A vaccines (1995-2006)



Since these vaccines are currently not reimbursed, these sales figures are thus for prescribed vaccines, presumably usually administered for travel-related prophylaxis, or in outbreak control situations. In Belgium recommendations from the Superior Health Council (SHC) (Hoge Gezondheidsraad (HGR) / Conseil Supérieur de la Santé (CSS)) date from 2002 and favor targeted immunization of high risk groups (e.g. travelers, patients with hepatitis C, or contacts of hepatitis A cases). Thus, there is no reimbursement from the social security system, except for a few groups at occupational risk for both hepatitis A and hepatitis B (see previous section). In 2006, The Fund for Occupational Diseases (FOD) (Fonds voor Beroepsziekten/ Fonds des Maladies Professionelles) also reported that 22427 positive decisions were taken for the reimbursement of vaccines containing an hepatitis A component (of these only 909 decisions were for monovalent hepatitis A, the remainder being for Twinrix (21518 or 96%)). (see website FOD http://www.fmp-fbz.fgov.be/index.htm)

Figure 3: Number of theoretical full schedules sold in Belgium (1995-2006)

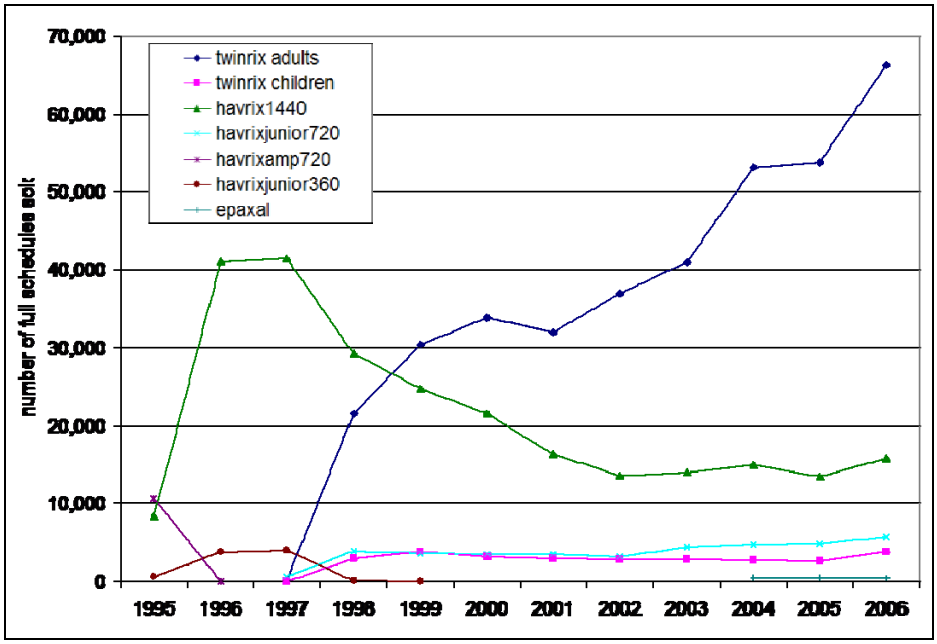


Figure 3 indicates how sales of full schedules (theoretical, based on sales figures of individual packages) may have evolved over time.

Knowing that the pediatric vaccines are indicated in Europe for children aged >1 year up to 15 years (included), we can infer from these data the order of magnitude of vaccination uptake rates in the Belgian population, distinguishing between adults and children (see table 8). Table 8 indicates that there is an increasing (though non-monotone) trend in uptake rates with time, showing 0.03% and 0.53% of children (1-15y) vaccinated in 1995 and 2006, respectively. There is a similar increasing trend for adults. Thus we can also infer that 0.23% and 0.95% of adults aged >15y were vaccinated each year. However, in view of the historical exposure of adults prior to 1995 (as shown in the 1993 and 2002 seroprevalence data below), and the nature of the recommended adult risk group vaccination strategies, it seems reasonable to assume that it would be very exceptional for elderly adults to be vaccinated against hepatitis A. Therefore table 8 also speculates that up to 1.4% of adults aged 16-55y and up to 1.9% of adults aged 16-45y could have been vaccinated with hepatitis A vaccine per year.

Table 8: Vaccine uptake estimates based on Belgian sales figures

full schedules sold per year of the various vaccine formulations by indicated age group												
	1995	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**
children (1-15y)	601	3,805	4,642	6,980	7,237	6,592	6,350	5,915	7,195	7,488	7,375	9,556
adults (>15y)	19,085	41,099	41,586	50,814	55,148	55,373	48,287	50,498	54,944	68,120	67,353	82,053
total nr of schedules	19,686	44,904	46,228	57,795	62,385	61,965	54,636	56,413	62,139	75,609	74,729	91,609
% of age group vaccinated per year												
	1995	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**
1-15y	0.03%	0.21%	0.26%	0.39%	0.40%	0.36%	0.35%	0.33%	0.40%	0.41%	0.41%	0.53%
>15y	0.23%	0.50%	0.50%	0.61%	0.66%	0.66%	0.58%	0.60%	0.65%	0.80%	0.79%	0.95%
16-55y*	0.34%	0.73%	0.74%	0.90%	0.97%	0.98%	0.85%	0.89%	0.96%	1.19%	1.18%	1.43%
16-45y*	0.44%	0.94%	0.95%	1.17%	1.27%	1.28%	1.12%	1.18%	1.29%	1.60%	1.58%	1.93%

*speculation, assuming that only relatively younger adults received hepatitis A vaccines, based on the recommended target groups and age-specific prevalence profiles (i.e. age groups with high proportions of immunes pre-vaccination are unlikely to still be vaccinated)

Assuming that all people who have been vaccinated since 1995 are still alive today, 708095 people (or 6.7% of all Belgian residents) received a full HAV vaccine schedule. Similarly, at the end of 2006, 73736 people between 2 and 27 years of age (or 2.3% of this age group), and 634359 people aged 16 years and over (or 7.4% of this age group) can be estimated to have received hepatitis A vaccination sometime between 1995 and 2006. Note that there is potential overlap between the latter and the former age group, which we cannot disentangle from these data. Clearly, the higher this overlap, the higher the percentage of vaccinated people in the former (more specific) age group. Note that we can again speculate about the upper age limit of the latter age group, implying that potentially 11% or 15% of people aged 16-55y or 16-45y, respectively, have been vaccinated.

Figures 4 and 5 show that there has been an important increase in public price, which was due to an increase in 2004 in the ex-factory cost per dose for all hepatitis A vaccines sold by GSK on the Belgian market.

Figure 4: Evolution of public prices per dose (1995-2006)

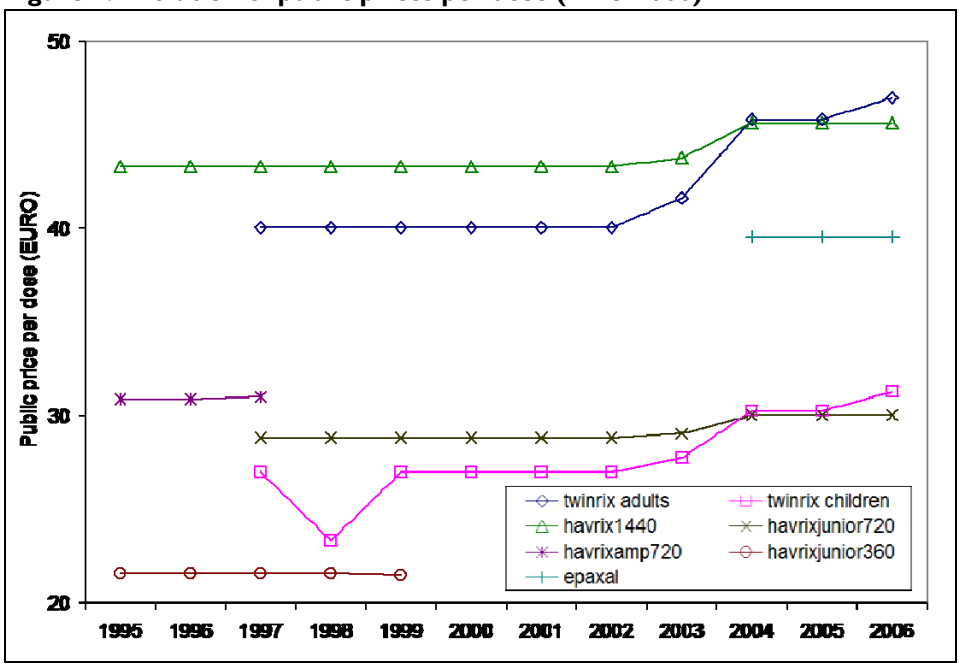
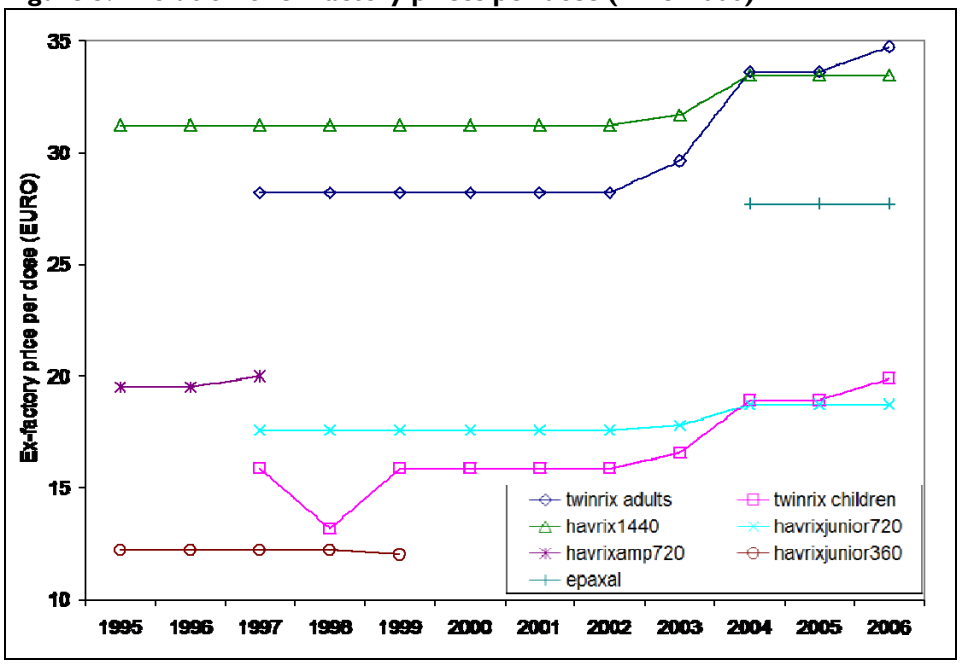


Figure 5: Evolution of ex-factory prices per dose (1995-2006)

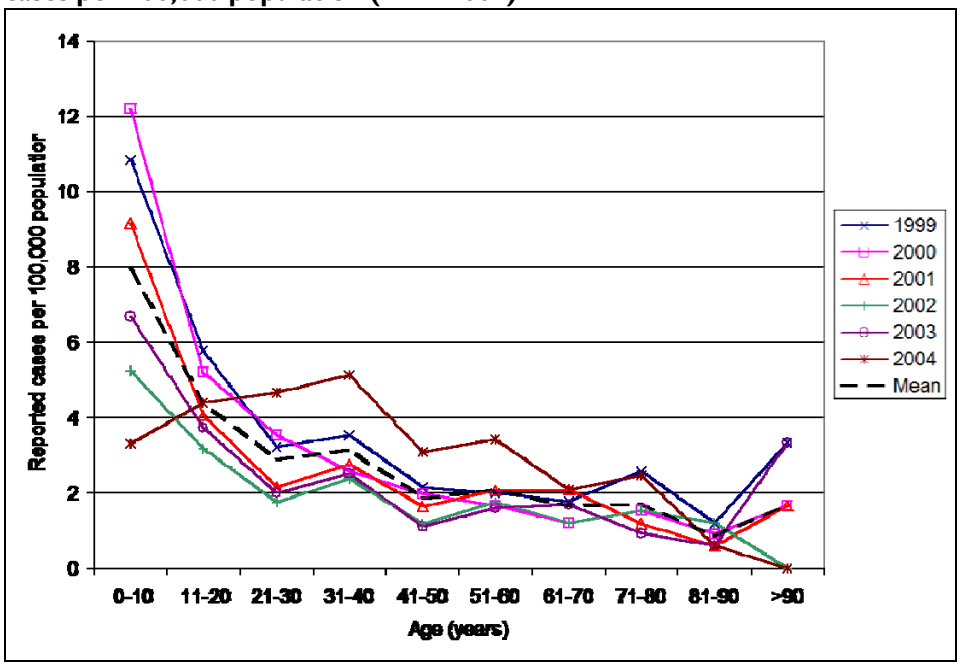


2.2 EPIDEMIOLOGY AND BURDEN OF HEPATITIS A IN BELGIUM

2.2.1 Incidence of reported lab confirmed hepatitis A cases in Belgium

In this section we show incidence data on voluntary reported lab confirmed hepatitis A cases. Clearly, one should be aware that the term "reported lab confirmed" means that these numbers only relate to what has been reported to the Institute of Public Health (IPH; Wetenschappelijk Instituut Volksgezondheid (WIV)/ l'Institut scientifique de Santé Publique (ISP)), with the restriction that this is only for cases for which a lab test was taken which was found to be positive for hepatitis A, and which was then reported. Clearly as such these data represent the proverbial tip of the iceberg. Other data sources are used in combination with these data to verify to which extent the age distribution and seasonality of cases, as observed here, holds.

Figure 6: Age-specific annual incidence of reported lab confirmed hepatitis A cases per 100,000 population (1999-2004)



It is expected that the incidence is geographically concentrated in urbanised areas, however, since t only the post code of the reporting laboratory is available for these data, it would remain speculative to divide these incidence figures further up according to post code. Furthermore, the outbreak data listed below show the geographical location of where the cluster of cases occurred, rather than where the samples were tested. It shows that in Flanders, the infection is geographically well dispersed between larger (Antwerpen, Gent, Brugge) and more rural areas (

Figures 6 and 7 illustrate that the age dependency of these reported lab confirmed cases has shifted over the period 1999-2004, with relatively more cases <10 years of age in the earlier versus the later years in this time period.

Figure 7: Age-specific incidence of reported lab confirmed hepatitis A cases per 1 million population per year (average 1999-2004)

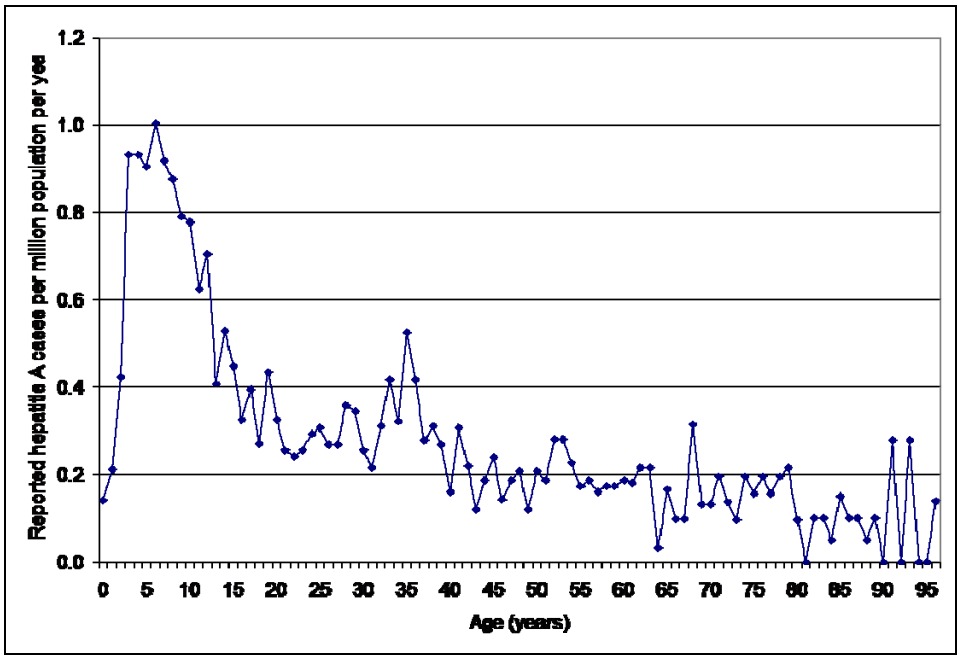


Figure 8 shows that there is no distinctive seasonality over all years combined, and **figure 9** confirms this, but clearly indicates that there has been a sudden increase in cases (reported and lab confirmed) in the third quarter of 2004, which is explained by a large outbreak in that quarter (see also below).

Figure 8: Weekly number of reported lab confirmed hepatitis A cases (average 1999-2004)

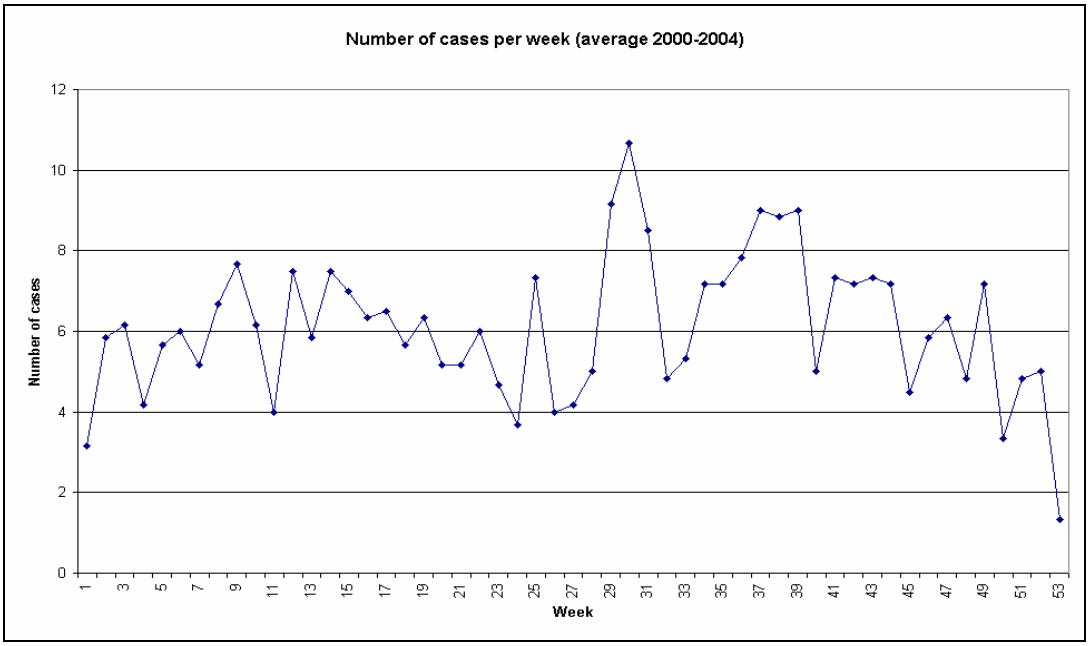
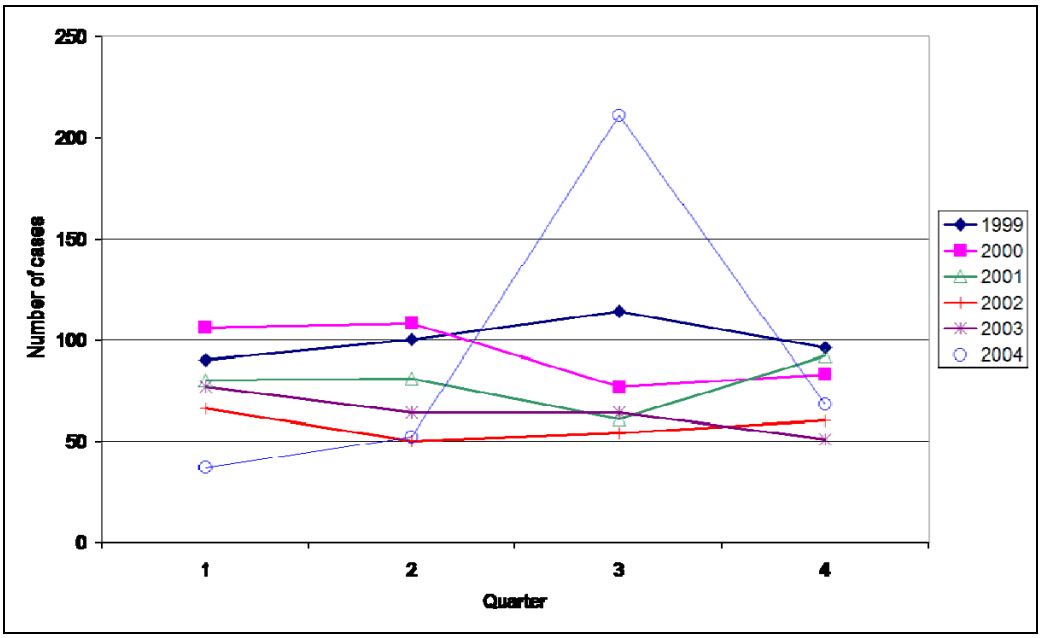


Figure 9: Quarterly number of reported lab confirmed hepatitis A cases (1999-2004)



2.2.2 Overview of recent outbreaks of HAV in the provinces of Antwerp, Limburg, West-Flanders, East-Flanders and Flemish Brabant

This section presents for all 5 Flemish provinces an overview of the clusters of HAV cases, which were recorded by the respective provincial health inspections.

The majority of outbreaks is confined to a number of detected cases ranging from 2 to 5. However a few outbreaks are considerably more extensive. For instance, between September and May 2006 in Mechelen 40 clustered cases were detected. The index case was a seven year old girl who went to Morocco for six weeks with her family and imported the virus from there. During the following 9 months the number of detected linked cases increased until 40 [100]

Close contacts within the family, school and kindergarten play a crucial role in the spread of hepatitis A infections. The most important risk-groups are close contacts within the family, men who have sex with men, children who reside in medical-pedagogic institutions and travellers to or visitors from high-endemic countries. Because of the latent infectious period and substantial probability of asymptomatic HAV disease, it is not straightforward to break the chain of transmission. Most outbreaks dissipate during a period of less intensive social mixing, if this is long enough to bridge the period of incubation, e.g. the summer holidays in schools, or simply when all susceptible persons of the close-contact-group have been immunised (through natural infection or through vaccination).

Tables 9, 10, 11, 12 and 13 present per province – to the extent to which this information was known or recorded - the date, number of cases, source, location, circumstances of each outbreak that took place in the five Flemish provinces.

It seems clear that most outbreaks are limited in detected cluster size. For instance, in provinces that could provide both small (<5 cases) and large (≥5 cases) clusters of cases, the median cluster size was 2, and the average was 7.4 and 3.7, respectively including and excluding the 1 very large food borne outbreak.

Table 9: Clusters of hepatitis A cases detected in the Province of West-Flanders (1999-2007)

Date	Source	Circumstances	Number of cases
18/09/1999	Consumption of raw oysters directly from sea during holiday	Family (2 cases: 2 brothers)	2
15/11/1999	?	family (2 cases: man and woman)	2
2/12/1999	?	Class (2 cases in same class)	2
6/03/2000	?	Family (2 cases: girl 6 years, girl 2 years)	2
28/03/2000	?	Class (2 cases (boy 5 years en girl 4 years)	2
17/10/2000	Indexcase: travel to Morocco	family (2 cases: brother 6 years en sister 8 years); Within school: 4 infants + mother and father from one of the infants + nanny; 3 kids from primary school	12
27/10/2000	Visit family member Morocco	family (3 cases: 2 brothers (2 years and 5 years) and sister (9 yearsr)	3
14/03/2001		School: 2 cases (living in West-Vlaanderen)	2
7/06/2001	?	Children daycarecenter: 2 kids	2
21/09/2001		Family: Grandfather; nephew and grandson	3
23/10/2001	?	Class (2 cases)	2
8/04/2002	?	Nanny and 1 of the children she was taking care of	2
27/04/2002	Child of adoption brought the disease from Haiti	Family (4 cases : mother and 3 children of adoption)	4
28/11/2002	School of one of the children	Family (2 cases : boy of 16 years, boy of 10 years); At the school of the youngest brother another case	3
3/03/2003	?	3 cases in the same school	3
28/03/2003	?	7 cases in the same school	7
23/04/2003	?	3 cases in the same school	3
17/06/2003	?	Family : 2 children and mother	3
20/08/2003	?	Mother and 2 sons	3
31/08/2003	?	14 cases around the same cradle(NL'kribbe')	14
1/10/2003	?	a couple	2
3/12/2003	?	5 children from the same school and father of one of the children	6
22/10/2004	?	8 cases in one MPI	8
22/08/2005	?	couple	2
3/01/2006	Pakistan	5 children from the same family	5
6/09/2006	Italy	3 people from the same family	3
23/11/2006	?	4 kids from one family, one classmate of them and one teacher	6
31/10/2007	?	Father-son-neighbour	3

Table 10: Clusters of hepatitis A cases detected in the province of Antwerp (2003-2007): only clusters of 5 cases or more

Date	Source	Location	Circumstances	Number of cases
18/03/2003	/	Merksem	Ski holiday Switzerland	5
11/09/2003	/	Merksem	Kindergarten	12
10/12/2003	/	Kontich	School	8
10/03/2004	/	Essen/Kalmthout	3 schools	5
1/7 – 31/8/2004PP [aPP]	/	Prov. Antwerp and Fl. Brabant	Food distributionPP [aPP]	271PP[aPP]
12/10/2004	/	Antwerpen	Family	5
11/04/2005	/	Mol	Family	5
Sep.2005-May 2006	/	Mechelen	Several schools and families	40
1/09/2006	/	Duffel	Family	5
14/12/2006	/	Antwerp	School	5
23/05/2007	/	Borgerhout	School	7
23/08/2007	/	Merksem + Fl. BrabantPP [bPP]	Trailer parkPP [PP]	14PP [PP]

[a]183 cases in Antwerp and 88 cases in Flemish Brabant, note this is the same cluster as reported for the province Flemish Brabant with date 5/07/2007
[b]however, this cluster seems not to be reported for the province Flemish Brabant

Table 11: Clusters of hepatitis A cases detected in the province of Limburg (2005-2007)

Date	Source	Location	Circumstances	Number of cases
12/01/2005	/	Beringen	School: 5 + sec. cases in the families	5PP[aPP]
2/10/2006	/	Koersel-Beringen	Family	3
19/10/2006	/	Kuringen-Hasselt	Family	4
9/01/2007	/	Hasselt	Restaurant/frying tavern: Father + son + 2 customers + wife of 1 client	5
25/09/2007	Index pt. made a holiday to Morocco	Houthalen	Family (Index pt. Made a holiday to Morocco): 3 + 1 friend	4

[a]at least five cases, the exact number is not known

Table 12: Clusters of hepatitis A cases detected in the province of Flemish Brabant (2001-2007)

Date	Source	Location	Circumstances	Number of cases
10/01/2001	?	Zaventem	School (2 children)	2
16/02/2001	?	Meise	Family (parent and child)	2
6/03/2001	?	Dilbeek	School (2 children)	2
9/10/2001	?	St-Pieters-Leeuw	School (3 children)	3
15/10/2001	?	Kessel-Lo	School (1 teacher and 2 children)	3
13/11/2001	?	Leuven	School (3 adults, 14 children)	17
21/11/2001	?	Wijgmaal	Family (1 adult and 2 children)	3
24/12/2001	?	Leuven	Creche (2 infants)	2
3/01/2002	?	Leuven	School (2 children)	2
5/03/2002	?	Wemmel	Family (2 adults)	2
19/09/2002	?	Vilvoorde	School (9 children in 3 schools)	5
29/11/2002	?	Eppegem	Family (3 adults)	3

31/01/2003	?	Brussel (Tovo involved fromt CLB)	Family (1 child at school and 1 infant creche)	2
29/08/2003	?	Diest	School (teacher and child)	2
30/09/2003	?	Brussel (Tovo involved fromt CLB)	School (4 children)	4
16/12/2003	?	Brussel (Tovo involved fromt CLB)	Family (parent and child)	2
5/07/2004PP [aPP]	FoodbornePP [aPP]	Grimbergen (+ Antwerp)PP [aPP]	Infected food distributionPP [aPP]	268PP [aPP]
16/12/2004 and 03/05/2005PP [cPP]	?	Vilvoorde	2 schools (common restaurant) (4 children + 1 child and its mother) and 5 families, 1school, 1MPI, 1creche involved (8 adults and 11 children)PP [cPP]	26PP [cPP]
25/11/2004 and 19/01/2005 and 07/02/2005PP [dPP]	?	Machelen	School and family (3 children + 1 child and mother + 1child); and family (1 adult and 2 children); and family (1 adult and 2 children)PP [dPP]	11PP [dPP]
1/12/2004	?	Kortenberg	Family (1 adult and child)	2
5/10/2004	Import	Halle	Family (3 children), import after visit North African home country	3
16/06/2004		Kortenberg	Family or MSM (2 men, partners)PP [bPP]	2
15/10/2005	Import	Merchtem	Family (2 adult), import ex Mexico	2
13/06/2005	?	Lubbeek	Family (2 adults and 2 children)	4
31/03/2005	?	Beersel	Family (2 adults and 2 children)	4
4/04/2005	?	Vilvoorde	Family (parent and child)	2
29/03/2004	brother of child for whom pt cared		Creche	2
22/03/2005	?	Keerbergen	Family (2 adults)	2
13/03/2005	?	Kapelle-Op-Den-Bos	Family (2 children)	2
14/02/2005	?	Grimbergen	Creche + family (2 children, 2 parents, 1 caretaker)	5
10/03/2005	?	Vilvoorde	School	2
14/04/2006	?	Korbeek-Dijle	Family (parent and child)	2
02/03/2006	?	St-Pieters-Leeuw	Partners (LAT)	2
03/03/2006	?	Herne	Family (parent and child)	2
04/01/2006	?	Tienen	Family (parent and child)	2
27/04/2007	?	Haacht	Partners (MSM?)PP [bPP]	2
16/05/2007	?	Brussel (Tovo involved fromt CLB)	Family (2 children)	2
02/05/2007	?	Averbode	School (3 children)	3
31/07/2007	?	Brussegem	Partners (MSM?)PP [bPP]	2
13/08/2007 and 04/07/2007PP [ePP]	?	caravan (oa Anderlecht, St Pieters Leeuw); caravan (Kessel-Lo)PP [ePP]	2 Families (each 2 children) and 1 childPP [ePP]	5
21/09/2007	?	Baal-Tremelo	Partners MSMPP [bPP] and family (child)	3
26/09/2007	?	Holsbeek	school (2 teachers)	2
27/09/2007	?	Rotselaar	Family (extended family)	2
30/11/2007	?	Lot	School	2
11/12/2007	?	Gooik	Family (extended family)	2

[a]183 cases in Antwerp and 85 cases in Flemish Brabant, note this is the same cluster as reported for the province Antwerp with date 1/7-31/8/2004

[b]MSM (Men who have Sex with Men): 2 male partners, but note: no information on sexual practice exists, so denotes only a possible transmission route based on sexual preference, besides family contact

[c]two clusters with different dates were put together as they are linked
[d]three clusters with different dates were put together as they are potentially linked
[e]two clusters with different dates were put together as they are potentially linked

Table 13: Clusters of hepatitis A cases detected in the province of East-Flanders (1999-2008). Dates represent dates of announcement of each case. Data presented are derived from individual data (i.e. per case in a cluster).

Date	Source	Location	Circumstances	Number of cases
26/08/1999	?	Wannegem-Lede	Couple	2
07/09/1999 en 27/09/1999	1PP[stPP] case: honeymoon Crete 2PP[ndPP] : from the spouse	Zevergem	couple	2
26/10/1999	1PP[stPP] case: from a friend, 2PP[ndPP] : Travel South-America	Bavegem (hometown of second "?")	1PP[stPP] case: friends; 2nd: late announcement	2
25/10/1999 en 12/11/1999	Guest AZG	Denderleeuw	couple	2
19/11/1999 en 01/12/1999 (2e en 3e) en 10/01/2000 en 9/02/2000 en 15/02/2000PP [aPP]	1PP[stPP] case: ? ; other cases: school?PP [aPP]	DendermondePP [aPP]		6PP [aPP]
26/09/2000	Montenegro	Gent	brothers	2
28/09/2000	1PP[stPP] case: Morocco; 2PP[ndPP] : Belgium	Gent	brother and sister (late announcement)	2
18/10/2000	1PP[stPP] case: Belgium, 2PP[ndPP] : Morocco	Erembodegem	brother and sister (late announcement)	2
18/10/2000	Turkey	Brakel	brothers	2
30/11/2000 en 01/12/2000 (last)	Belgium	Gent	1 brother and 2 sisters	3
05/12/2000 en 13/02/2001-28/02/2001 en 30/07/2001PP [aPP]	1PP[stPP] six cases: school?; 7th: via son; 8th: school? Case dec. 2000; 9th: via family; 10th: school?idem; 11-13th:school?; 14th-18th: Late notification, children go to same schoolPP [aPP]	Gentbrugge, except 7the and 8PP[thPP] case: GentPP [aPP]	6 first cases: announced by the same CLB-doctor; 7th: father and son, 9th: family of the case 9040 (father and son); 11th:sisters; 14th-18th: familyPP [aPP]	18PP [aPP]
28/02/2001-06/06/2001	1PP[stPP] case:?, 2nd and 3th via sister, 4th via brother	Gentbrugge	family	4
16/05/2001 en 11/06/2001	1PP[stPP] case:Morocco, 2PP[ndPP] : via mother	Gentbrugge	family	2
2/10/2001	Turkey	Gent	brother and sister	2
4/02/2002	Belgium?	Kruishoutem	brother and sister	2
03/04/2002-05/04/2002	Belgium?	Sint-Niklaas	2 sisters and 1 brother	3
30/04/2002	Belgium?	Eeklo	couple	2
12/07/2002 en 19/07/2002	Belgium?	zaffelare	couple	2
27/08/2002-12/09/2002	1PP[stPP] case: Morocco; other cases: Morocco?	Sint-Niklaas	gezin	4
21/11/2003	1PP[stPP] case: from mother, 2PP[ndPP] : ? (=mother)	Machelen	late announcement mother	2

30/03/2004	Belgium? Father, mother, daughter	Lokeren	late announcement mother	3
17/08/2004-08/09/2004	1PP[stPP] case: Kenya, 2PP[ndPP] : mother; 3th: father and ex; 4th: friend from father	Beveren-Waas	Beveren-Waas	4
10/09/2004-01/10/2004	1st three cases: Afghanistan, 4th: Afghanistan?	Melsele	family	4
5/11/2004	Belgium?	Ronse	family	2
21/04/2005	Belgium?	Bavegem	brother and sister	2
27/07/2006 en 17/02/2006	Belgium?	Lokeren	couple	2
11/09/2006 en 05/10/2006	1PP[stPP] case: Belgium?; 2PP[ndPP] : father	Waasmunster	family	2
05/03/2007 en 02/05/2007	1PP[stPP] case:?, 2PP[ndPP] : school	Lovendegem		2
21/09/2007-5/12/2007 en 03/01/2008PP[aPP]	1PP[stPP] case: caravanpark?, 2nd:?, 3rd and 4th: caravanpark, 5th: presumably son (°2001) H. Hartschool, 6th: childcarer H. Hartschool; 7th :presumably daughter (medical doctor did not comply to the vaccination advice)PP[aPP]	Dendermonde, but 2nd and 7th case from LebbekePP[aPP]	1PP[stPP] case: Romagipsy (caravanpark without sanitary); 2nd: H. Hartschool; 3rd: daughter H. Hartsch. (1 month ago, with fever and now immune, °2001), 4th: sister of 07/11/1982 (live together); 5th: daddy; 7th: comes from the mother of the 19/10/2007 case)PP[aPP]	7PP[aPP]
03/10/2007 en 05/10/2007	?Belgium	Dendermonde	Brother and sister (no contacts via H. Hartschool or caravanpark)	2
26/02/2008 en 15/04/2008	1PP[stPP] case: Vietnam, 2nd: België	Belsele (Sint-Niklaas)	1PP[stPP] case: parents and child go to live in Vietnam, back from first visit; 2PP[ndPP]: lived with this uncle (was not known when announcement of the first casus)	2
21/03/2008 en 08/04/2008PP[bPP]	Family in BrusselsPP[bPP]	RonsePP[bPP]	link with cluster in Brussels (2 cases)PP[bPP]	2PP[bPP]
01/07/2008PP[bPP]	Works as a sport teacher in a school in Sint-JansmolenbeekPP[bPP]	DendermondePP[bPP]	Link Flemish-brabant (? cases)PP[bPP]	?PP[bPP]

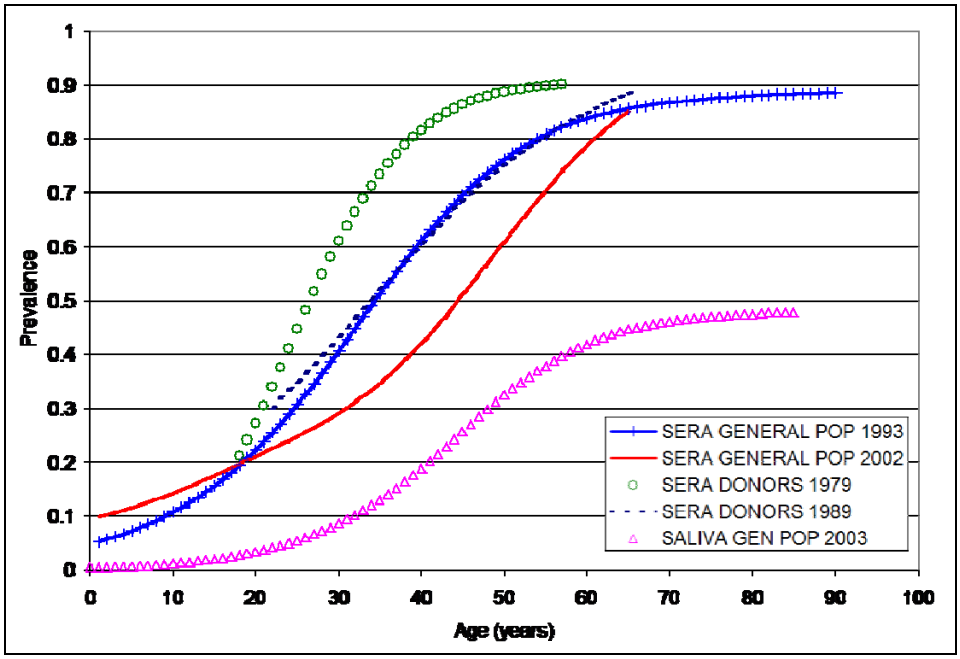
[a]clusters with different dates were put together as they are linked
[b]probably linked with a cluster in Flemish Brabant.

2.2.3 Seroprevalence

A number of cross sectional prevalence datasets are available for Belgium, of which four are based on sera, collected and archived under the direction of Prof Pierre Van Damme at the University of Antwerp, in collaboration with the WIV (obtained in 1979 in first time blood donors, in 1989 in first time blood donors, 1993-1994 in the Flemish general population[101], 2002-2003 in the general Belgian population (unpublished)). One other database was collected and archived under the direction of WIV and contains saliva samples (obtained in 2003-2004 in the general Belgian population [102]).

Shkedy et al[103], Shkedy et al[104], Namata et al[105] and Hens et al [106] developed specific methods to estimate seroprevalence profiles and their confidence intervals, and derive the single, joint and conditional force of infection from such data. We explored these methods for the HAV and HCV datasets, and we report on some of the results in this section.

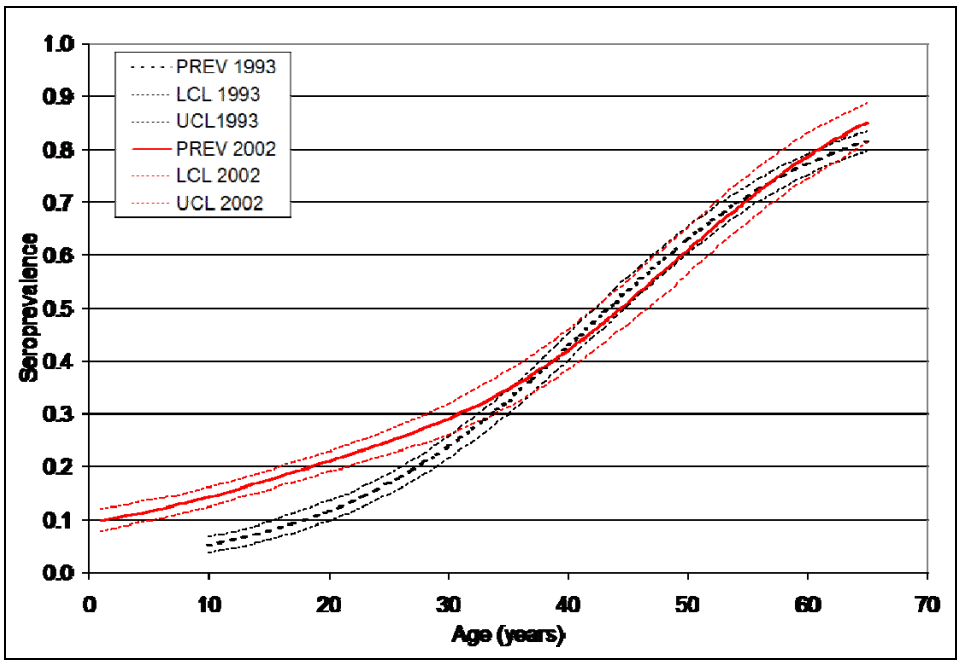
Figure 10: Age-specific hepatitis A prevalence in Belgium at different time points from population based samples obtained from sera and saliva.



Unsurprisingly, figures 10 and 11 show that the assumption of time homogeneity is violated in relation to HAV in Belgium (as in the rest of the developed world). Indeed there has been a clear decline in immunity in all adult age groups (>18 y) from 1979 to 1989 and 1993 (described in Beutels et al[101, 107]), and further still from 1993 to 2002. The sample based on saliva represents a study conducted by the WIV in 2003. It clearly indicates a much lower overall prevalence level (by looking at the large difference with the 2002 serum based sample), which is believed to be due to a biased sample (with underrepresentation of people who were immune, since these had no incentive to participate in the study).(personal communication dr Sophie Quoilin, WIV, 2008). Clearly, most relevant for the explorations in the current report are the serum samples from 1993 and 2002, which were assembled and analysed using similar methods and tests (HAV-Elisa for the 2002 serum sample; RIA Elisa for the 1993 sample; a formal comparison of these tests for hepatitis A is not available).

The comparison of the 1993 and 2002 data sets is shown differently in figure 11 by shifting the 1993 observations such that the observations show different 1993 and 2002 data for the same statistical age groups (i.e. age as observed in 2002).

Figure 11: Shifted age-specific hepatitis A seroprevalence in 1993, compared with age-specific hepatitis A seroprevalence in 2002, with 95% confidence limits.



It can be seen that persons aged 38y (30y with confidence limits) and more in 2002 did not gain any noticeable immunity against hepatitis A between 1993 and 2002 (i.e. neither from natural infection nor from the vaccine). Persons aged 10 to 30 years have, on average, gained non-negligible immunity (either through natural infection or through vaccination). Note that this could concur with the age-specific notified caseload described in section 2.2.1.

Figure 12 shows the conditional seroprevalence and force of infection for hepatitis A, in people infected with hepatitis C.

Figure 12: Seroprevalence and force of infection for hepatitis A, conditional on hepatitis C, based on Belgian seroprevalence data from 1993

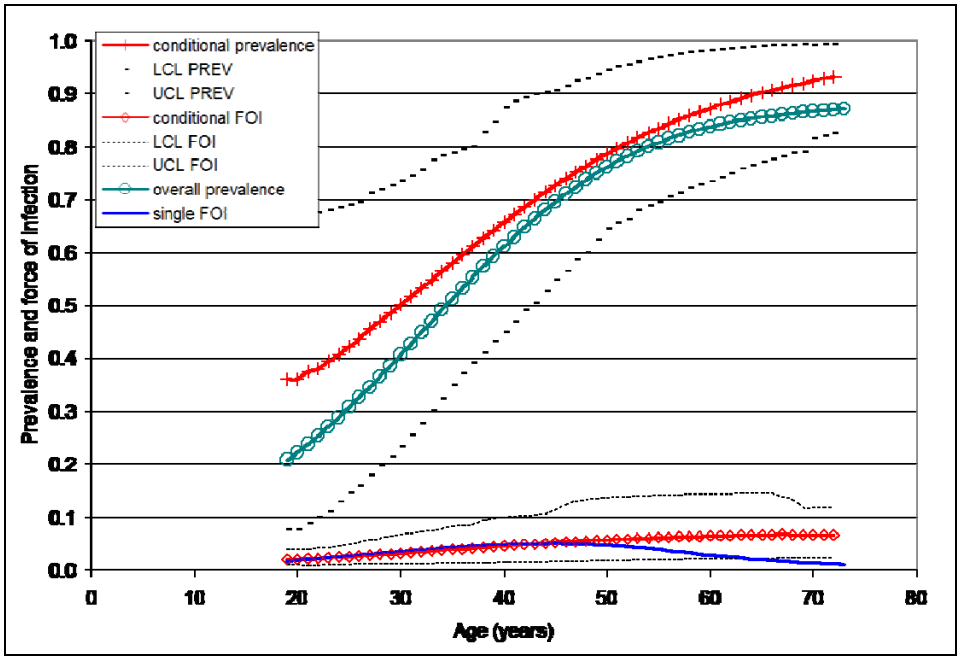


Figure 12 indicates that there is no significant difference in HAV seroprevalence conditional on a previous hepatitis C infection. The derived force of infection shows a slightly greater , though non-significant force of infection (FOI), for people who have previously been infected with hepatitis C versus the general population.

In what follows we will not focus the analyses on patients with chronic HCV, but on the general population at risk of HAV (and treatment costs have been defined accordingly). Since vaccinating HCV positive patients against hepatitis A is considered good practice with a limited budget impact, this will not be explicitly modelled as part of this report.

2.2.4 Hospitalization data (MKG/RCM)

The registration of Minimal Clinical Data (MCD[2]) is mandatory for every hospital in Belgium since 1991. This means that for each hospitalized patient, information such as birth date, sex, postal code of domicile and other information such as length of hospital stay (LOS), hospital ward and bed type occupation etc., has to be recorded, along with ICD-9-CM[3] encoding of relevant diagnoses as well as diagnostic and therapeutic procedures performed. Diagnosis and procedure codes are collected per attended hospital department, each coding for one primary and several secondary diagnoses. This inevitably results in a possible redundancy for certain stay specific diagnosis codes causing code frequency counts sometimes to exceed stay counts. (see section 2.2.4.1.) After stripping of direct patient-identifying information, records have to be sent biannually to the federal Ministry of Health (MoH[4]). Here all department registrations are concatenated with assignment of the primary diagnosis of the whole stay, determinant for the APrDRG-grouper[5] software.

Since 1997 the MCD records are afterwards linked to the Minimal Financial Data (MFD[6]), yearly transmitted by the national health insurance companies (HIC) to the NISDI and assembling the remuneration costs of each hospital stay. MCD-MFD linkage is performed by a legally instituted 'Technical Cell' and requires separately sent correspondence tables containing for each identifiable hospital stay a unique patient pseudonym created by two separately executed hashings: the first by the hospital or HIC respectively and the second by an appointed security advisor of the MOH[7]. Linkage process takes about 2 years to completion and full validation[8]. Linkage percentages increased over the years and exceed nowadays 95% overall[9]. This means that the relationship between treated pathology and the costs to the health care system can be studied, at least for classical hospitalizations.

The MKG database also contains records of 'one day' admissions (i.e. patients not staying overnight in the hospital) and outpatients' treatments requiring hospital facilities, however without coupling with billing data yet[10]. These records were not included in our data transmission request.

The advantage of the coupled MKG-MFG data is that it is obligatory for all hospitals (MKG) and all national health insurance companies (MFG). However, one should keep in mind that we do not know how accurate each hospital reports the obligatory MKG data, nor how reliably the MFG data are gathered.

In this section we report on data obtained from the MKG-MFG for the period 2000-2004[11].

---

2 MKG = 'Minimale Klinische Gegevens / RCM = Résumé Clinique Minimum'

3 International classification of diseases, version 9, clinical modification (WHO)

4 Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu / Service Public Fédéral Santé publique, Sécurité de la Chaîne alimentaire et Environnement

5 All Patient refined Diagnostic Groups, version 15.0

6 MFG = 'Minimale Financiële Gegevens / RFM = Résumé Financier Minimum'

7 Procedures approved by the Belgian Privacy Commission

8 Actually 2005 is the last year for linked MCD-MFD records

9 Expressed as the fraction of the number of stays in MFD data as denominator; staycounts in MFD are always less than staycounts in MCD data since those cover all hospital stays, wether or not they were at the expense of the NISDI.

10 Planned for data 2006.

11 2005 not yet available at moment of data request.

These are based on data extractions of hospitalizations with a primary or secondary code of (ICD9):

- 070.0 Viral hepatitis A with hepatic coma
- 070.1 Viral hepatitis A without mention of hepatic coma

Based on above criteria a primary total of 1,843 stays was retrieved (**Table 14**). APrDRG-distribution is presented in **Table 15**. Only 830 stays (741 with MKG-MFG linkage) were in the appropriate "APrDRG 283": disorders of liver except malignancy, cirrhosis or alcoholic hepatitis.

Severity index is a severity of illness subclassification based on secondary diagnoses; counts for APrDRG 283 are summarized in **table 16**.

Coma counts are in **table 17**. Counts include not only 0700 diagnostic code but also any combination of 0701with 5722 (hepatic coma)

Table 14: Stay and patient counts 2000-2004

Year	2000	2001	2002	2003	2004	2000-2004
Patients	409	356	329	288	343	1.725
Stays	439	374	352	306	372	1.843

Table 15: MDC[12] and APrDRG distribution for hepatitis A coded stays

MDC	APrDRG	All stays	Linked MCD-MFD
MDC 7 Medical	283 - DISORDERS OF LIVER EXCEPT MALIG, CIRRHOSIS OR ALCOHOLIC HEPATITIS	830	741
	284 - DISORDERS OF THE BILIARY TRACT	18	17
	280 - CIRRHOSIS & ALCOHOLIC HEPATITIS	13	12
	281 - MALIGNANCY OF HEPATOBILIARY SYSTEM & PANCREAS	11	11
	282 - DISORDERS OF PANCREAS EXCEPT MALIGNANCY	8	8
MDC 7 Surgical	263 - LAPAROSCOPIC CHOLECYSTECTOMY	20	19
	260 - PANCREAS, LIVER & SHUNT PROCEDURES	8	5
	262 - CHOLECYSTECTOMY EXCEPT LAPAROSCOPIC	7	7
	261 - MAJOR BILIARY TRACT PROCEDURES	4	4
	264 - OTHER HEPATOBILIARY & PANCREAS PROCEDURES	2	1
Other MDC 7		91	84
Other MDC		922	817
Totals		**1.843**	**1.642**

Table 16: Severity index counts for linked stays in APrDRG 283

APrDRG 283 Severity	Stays	Patients
1 = Minor	441	432
2 = Moderate	230	229
Subtotal 1 + 2	**671**	**661**
3 = Major	55	54
4 = Extreme	15	14
Subtotal 3 + 4	**70**	**68**
Totals	**741**	**728**

12 Major Diagnostic Categories; MDC 7 = disorders of the digestive system

Table 17: Counts per primary or secondary diagnosis, without or with coma, linked stays

APRDRG 283		Severity	Stays	Patients
No coma	Primary Hepatitis A	Minor	435	426
		Moderate	211	210
	Secondary Hepatitis A	Minor	6	6
		Moderate	9	9
Coma			10	10
		Totals	**671**	**661**

2.2.4.1 Data categorisation based on crude codes (without exclusions)

Number of hospitalizations and duration of stay

Figures 13 and 14 show the incidence and age distribution of hospitalizations coded with HAV without hepatic coma, in primary or in secondary diagnosis. Patient age was calculated by substracting year of birth from registration year. One stay out of the total of 1843 proved to have a code 0700 as primary diagnosis and a code 0701 as secondary code.

It shows that the incidence of HAV hospitalizations without hepatic coma remains fairly stable up to age 70, presumably because after that age, the overall probability of hospitalization increases due to age-related frailty.

Figure 13: Number of hospitalizations coded with Hepatitis A (primary or secondary diagnosis) without coma per age (2000-2004) – N=1801

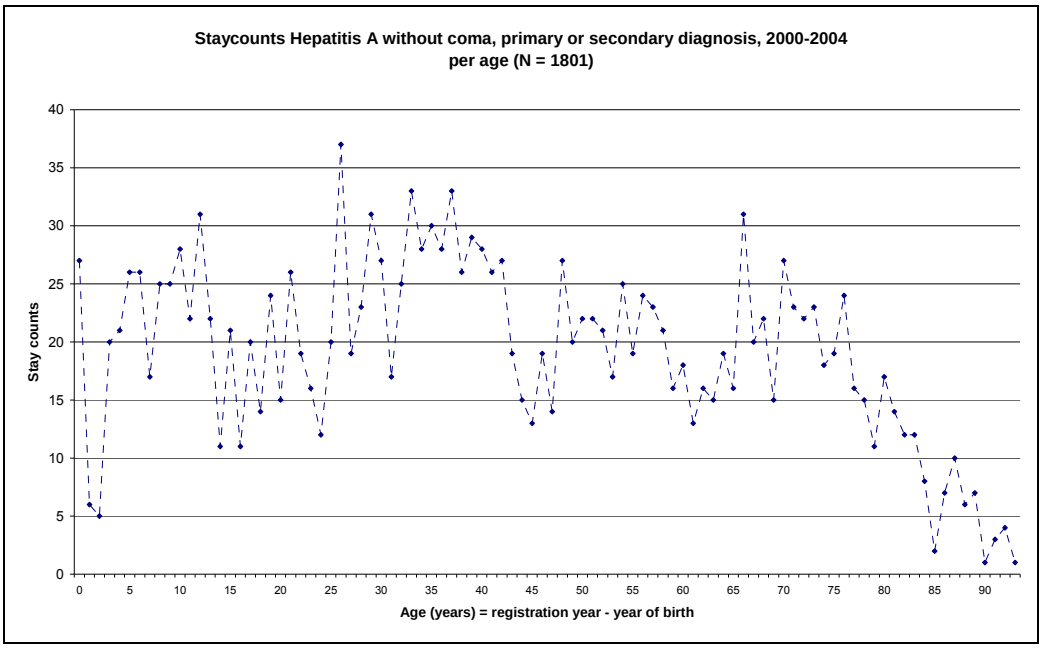
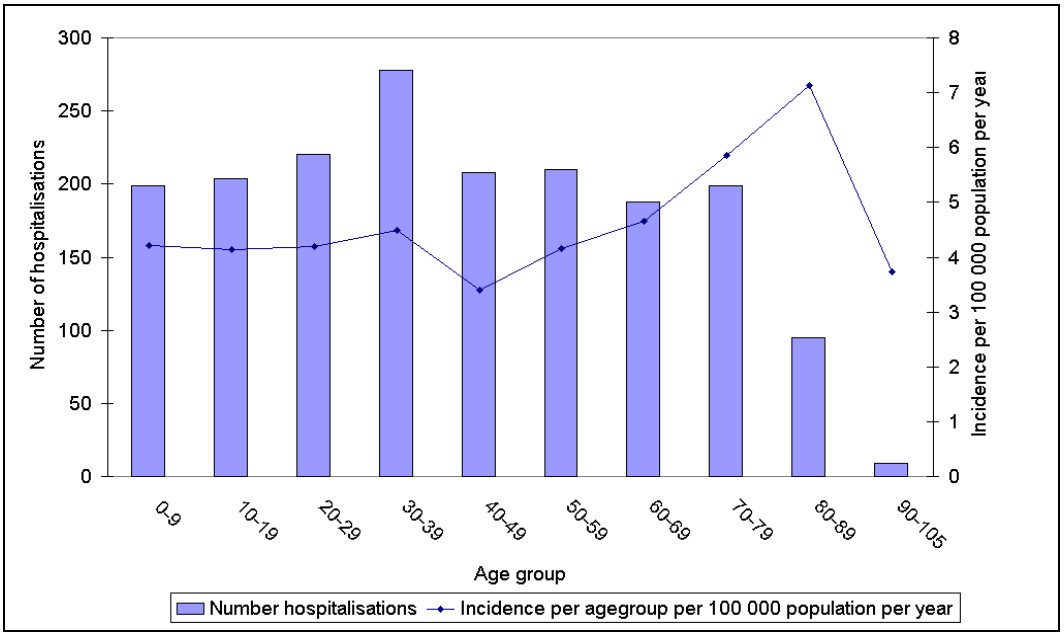
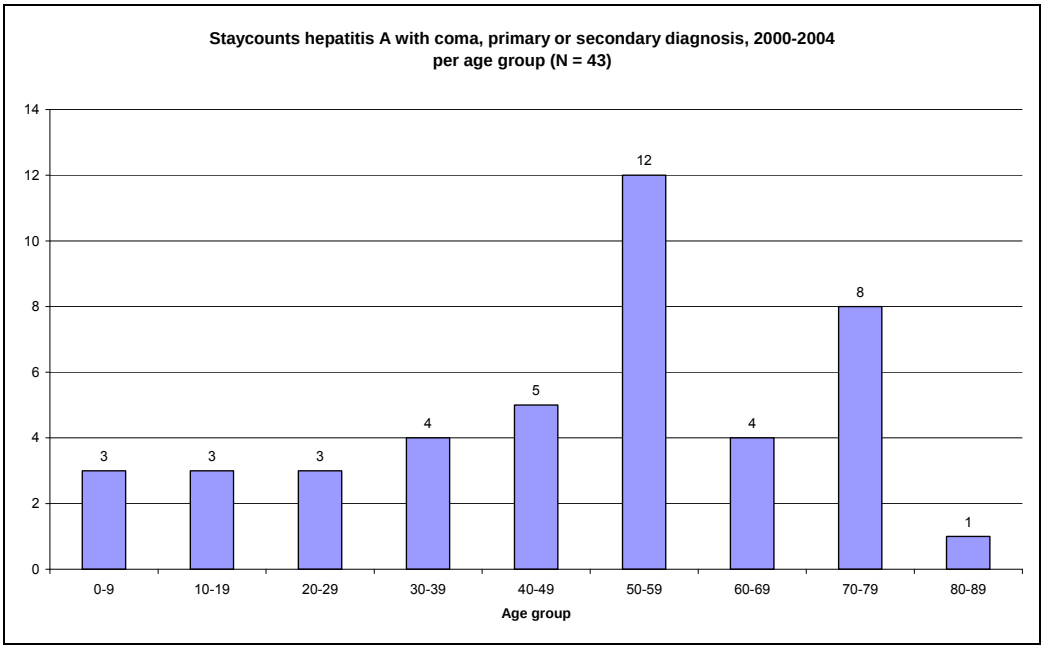


Figure 14: Age-specific number and incidence of hospitalizations coded with hepatitis A (primary or secondary diagnosis) without hepatic coma per age group (2000-2004)



Also hospitalizations with hepatic coma occur in all age groups, but most frequently between 50 and 59, as well as between 70 and 79, when the probability of coma may be higher for other reasons than hepatitis A (figure 15). These aspects are further explored below.

Figure 15: Age-specific number of hospitalizations coded with viral hepatitis A (primary or secondary diagnosis) with hepatic coma (2000-2004) – N=43



Tables 18, 19 and 20 show all hospitalizations in Belgium during the years 2000-2004, coded with hepatitis A.

All these admissions were divided into 4 categories, distinguishing those with or without hepatic coma as well as codes occurring in primary or secondary diagnostic fields.

All admissions with coma as primary diagnosis could, in theory, be considered as fulminant hepatitis.

However, further in-depth analyses (below) will determine whether the hepatitis A attributable hospitalizations are in line with the crude division of these codes presented in tables 18, 19 and 20. What needs to be investigated is whether hepatitis A was at the basis for the hospital admission for these patients. Particularly in the group 'HAV without coma in secondary diagnosis' it is expected that there are many patients with atypical or asymptomatic hepatitis A, and a plethora of underlying illnesses (see appendix C) or even HAV-immune-patients due to a former infection or vaccination.

Therefore, there is a need to examine the proportion of cases with HAV and other liver and non-liver related diagnoses (such as alcoholism, diabetes, etc…) since this distorts the age distribution of cases, the length of stay (LOS), and the costs for hospitalization. Such distortions are less likely when hepatitis A was coded in a primary diagnostic field. Indeed, it can be seen that the average and median LOS is similar for hospitalizations with a primary code of hepatitis A with or without coma (see table 19).

Table 18: Hepatitis A encoding frequencies (2000 – 2004)

		coma (primary diagnosis)		coma (secondary diagnosis)		without coma (primary diagnosis)		without coma (secondary diagnosis)		all HAV hospitalizations	
		code frequency	%	code frequency	%	code frequency	%	code frequency	%	code frequency	%
total number		18	100	26	100	795	100	1015	100	1854	100
number of hosp. Per region	*Flanders*	7	38,9	13	50,0	457	57,5	393	38,7	870	46,9
	Wallonia	5	27,8	7	26,9	205	25,8	459	45,2	676	36,5
	Brussels	6	33,3	6	23,1	122	15,3	143	14,1	277	14,9
	Invalid	0	0,0	0	0,0	11	1,4	20	2,0	31	1,7
number of hosp. Per nationality	*Belgian*	13	72,2	21	80,8	643	80,9	802	79,0	1478	79,7
	EU-inhabitant	2	11,1	2	7,7	25	3,1	48	4,7	77	4,2
	Non-EU	3	16,7	3	11,5	58	7,3	70	6,9	134	7,2
	Unknown	0	0,0	0	0,0	69	8,7	95	9,4	165	8,9
number of hosp. Per age-group	*0-9*	1	5,6	2	7,7	149	18,7	50	4,9	202	10,9
	10-19	3	16,7	1	3,8	169	21,3	35	3,4	208	11,2
	20-29	1	5,6	2	7,7	135	17,0	85	8,4	223	12,0
	30-39	2	11,1	2	7,7	138	17,4	140	13,8	282	15,2
	40-49	4	22,2	1	3,8	86	10,8	122	12,0	213	11,5
	50-59	5	27,8	7	26,9	47	5,9	163	16,1	222	12,0
	60-69	0	0,0	4	15,4	42	5,3	146	14,4	192	10,4
	70-79	2	11,1	6	23,1	19	2,4	180	17,7	207	11,2
	80-89	0	0,0	1	3,8	10	1,3	85	8,4	96	5,2
	90-105	0	0,0	0	0,0	0	0,0	9	0,9	9	0,5
number of deaths	*Total*	3	16,7	4	15,4	3	0,4	38	3,7	48	2,6
	Flanders	2	11,1	3	11,5	1	0,1	16	1,6	22	1,2
	Wallonia	0	0,0	0	0,0	0	0,0	14	1,4	14	0,8
	Brussels	1	5,6	1	3,8	2	0,3	8	0,8	12	0,6

Table 19: Duration of stay of hospitalizations (2000 – 2004) (in days)

		Coma (Primary diagnosis)		Coma (secondary diagnosis)		Without coma (primary diagnosis)		Without coma (secondary diagnosis)		All hospitalizations	
		average	median	average	median	average	median	average	median	average	median
Average and median		5,0	4,0	27,6	13,5	5,4	4,0	12,8	7,0	9,8	5,0
average and median per age-group	*0-9*	3,0	3,0	4,5	4,0	3,8	3,0	5,4	4,0	4,2	3,0
	10-19	5,3	4,0	4,0	4,0	4,1	4,0	8,6	5,0	4,9	4,0
	20-29	1,0	1,0	8,5	8,5	4,5	4,0	7,8	4,0	5,8	4,0
	30-39	5,0	5,0	23,0	23,0	4,9	4,0	10,2	6,0	7,7	5,0
	40-49	4,0	3,0	14,0	14,0	5,9	4,5	9,5	5,0	8,0	5,0
	50-59	4,4	4,0	29,9	28,0	7,8	6,0	11,7	8,0	11,3	7,0
	60-69	0,0	0,0	67,5	16,5	10,1	6,0	12,5	7,0	13,1	7,0
	70-79	10,0	10,0	23,5	19,0	11,4	7,0	16,7	12,0	16,3	11,0
	80-89	0,0	0,0	7,0	7,0	18,5	11,5	27,2	17,0	26,1	16,5
	90-105	0,0	0,0	0,0	0,0	0,0	0,0	20,1	14,0	20,1	14,0
average and median per region	*Flanders*	6,1	6,0	21,0	17,0	5,1	4,0	12,8	7,0	8,8	5,0
	Wallonia	3,8	3,0	17,7	13,0	6,2	4,0	12,3	7,0	10,5	6,0
	Brussels	4,7	4,0	53,3	10,5	5,0	4,0	14,1	7,0	10,8	5,0
average and median per nationality	*Belgian*	5,5	4,0	29,1	14,0	5,5	4,0	13,0	7,0	9,9	5,0
	EU-inhabitant	1,5	1,5	42,0	42,0	6,1	6,0	10,8	6,0	9,8	6,0
	Non-EU	5,3	4,0	7,3	8,0	4,8	3,5	11,2	7,0	8,2	5,5

In table 18 the total number of hospitalizations of each diagnosis was categorized according to nationality (Belgian, EU-inhabitant or Non-EU-inhabitant), the Belgian region at which the patient is domiciled TPTP[13]PTPT, and also according to the age group to which the patient belongs. Finally the number of hospitalizations ending in death was analysed according to region.

During the 5 years studied there were 1843 hospitalizations due to Hepatitis A. The occurrence of symptomatic Hepatitis A in the three different regions is more or less proportionate with the size of the regions. Note that a sizeable proportion of hospitalizations are linked to Non-EU-inhabitants.

When we examine the distribution according to age group we find more hospitalizations in the younger age groups, especially for hepatitis A without coma in primary diagnosis. A possible explanation is that paediatricians and GPs upon presentation of an icteric case in a child, are more likely to refer to hospital than a GP or gastroenterologist consulting an icteric adult patient. Despite the well documented inverse relationship between the probability of symptomatic and icteric hepatitis A infections and age at infection, there are also children admitted with hepatitis A with coma as a primary diagnosis.

About 2,6 % of all hospitalizations ended in death. As expected, the proportion deceased is larger for a diagnosis with than without coma. For hospitalizations without coma in secondary diagnosis the number of deaths is much higher but this is at least partly attributable to other underlying illnesses, which are further analysed below.

Table 19 summarizes the LOS of all hospitalized cases from 2000 to 2004, also according to the four fields of diagnosis. The difference in median and average can be explained by some outliers. The average LOS with HAV is approximately 10 days, while the median amounts to 5 days.

When we examine the primary diagnoses we can see that there is not much difference in duration of stay between hospitalizations with and without coma. Apparently the LOS does not increase significantly for coma patients, who are likely to die, or to be transferred for transplantation, or to recover quickly.

As expected, the LOS increases with age, i.e. when underlying illnesses become more prominent. Note that for admissions with hepatitis A coded with secondary diagnosis, the proportion aged 60 years or older amounts to 41% without coma, and 42% with coma. This clearly digresses from codes under primary diagnosis, where the proportion aged 60 years or more is 11% with and 9% without coma.

For patients with coma there seems to be a rather large difference in LOS between the regions but this may be due to the small number of cases in this category. In table 20 the age distribution is specified per region which can help to explain some of the results. In general the duration of stay is very similar between regions and nationalities.

[13] The region has been derived from the areacode ('arrondissementscode') to which the patient belongs. This is detailed in appendix D.

Table 20: Hepatitis A encoding frequency, number of patients hospitalized and incidence by age and diagnosis (2000-2004)

	coma (primary diagnosis)			coma (secondary diagnosis)			without coma (primary diagnosis)			without coma (secondary diagnosis)			All patients and hospitalizations		
AGE	Frequency	patients	incidence	frequency	patients	incidence	Frequency	patients	incidence	frequency	patients	incidence	Frequency	patients	incidence
0-9	1	1	0.01696	2	1	0.016968	149	138	2.34163	50	47	0.797513	202	185	3.139146
10-19	3	2	0.03244	1	1	0.016224	169	159	2.57964	35	33	0.535399	208	193	3.13127
20-29	1	1	0.01528	2	2	0.030563	135	126	1.92548	85	79	1.207246	223	200	3.056318
30-39	2	1	0.01290	2	2	0.025804	138	122	1.57401	140	122	1.574015	282	243	3.135129
40-49	4	4	0.05232	1	1	0.013082	86	80	1.04658	122	109	1.425976	213	191	2.498728
50-59	5	5	0.07921	7	5	0.079211	47	45	0.71289	163	150	2.376328	222	202	3.200121
60-69	0	0	0	4	4	0.079353	42	40	0.79352	146	135	2.678152	192	174	3.45184
70-79	2	2	0.04708	6	6	0.141242	19	18	0.42372	180	165	3.884153	207	190	4.472661
80-89	0	0	0	1	1	0.060001	10	10	0.60000	85	80	4.80006	96	91	5.460068
90-105	0	0	0	0	0	0	0	0	0	9	9	2.987859	9	9	2.987859

Table 21: Summary of Hepatitis A encoding frequencies per year

		2000	2001	2002	2003	2004
Number per age-group	0-9	71	54	31	29	17
	10-19	64	39	38	29	38
	20-29	57	48	39	34	45
	30-39	77	51	63	46	45
	40-49	33	49	41	36	54
	50-59	39	42	35	46	60
	60-69	44	35	47	19	47
	70-79	30	38	38	54	47
	80-89	24	19	21	12	20
	90-105	4	0	2	3	0
Number per region	Flanders	210	167	155	135	203
	Wallonia	147	138	150	115	126
	Brussels	75	65	45	53	39
	Invalid	11	5	5	5	5
Number per nationality	Belgian	342	270	284	258	324
	Eu-inhabitant	18	16	12	14	17
	non-EU	31	40	25	22	16
	unknown	52	49	34	14	16

Table 20 compares the Hepatitis A encoding frequency with the number of different patients hospitalised with hepatitis A as one of the diagnostic codes.

The numbers indicate that for every diagnosis a few patients were hospitalised several times, probably due to complications of the disease after dismissal from the hospital. Mostly however there was only one hospitalization per patient. The incidence for HAV without coma in primary diagnosis is higher for the younger age groups. For HAV with coma in primary diagnosis the incidence is higher in the older age groups.

Table 21 shows the Hepatitis A encoding frequency specified per year. The distributions are approximately equal for the years 2001- 2003 but slightly different for 2000 and 2004. For these years especially in Flanders there was a high number of hospitalizations. In the year 2000 there were significantly more hospitalizations in the youngest age groups. The majority of hospitalizations is attributable to Belgians.

Cost of hospitalizations with hepatitis A in one of the diagnostic codes

Table 22 is the summary of the costs of all hospitalizations with Hepatitis A encoding. These data are expressed in prices of 2004 by applying Consumer price indices (CPIs) for hospital services. What they reflect is the cost of a hospitalization where one of the diagnoses (primary or secondary) was Hepatitis A and therefore not necessarily the cost attributable to HAV.

The total cost of all hospitalizations amounts to 5,167,294 € over a 5 year period, or about €1 million per year. The average cost of a hospitalization with Hepatitis A involved is 3,146 € and the median cost is 1,527 €. Here also a number of outliers exert a strong influence on the average. Upon first examination, as expected, costs are higher for older age groups. Hospitalizations with coma are also more expensive than without coma.

Table 22: Crude costs of hospitalizations with one of the codes reported as hepatitis A (2000- 2004) (expressed in 2004 €[14])

		Coma (Primary diagnosis)		Coma (secondary diagnosis)		Without coma (primary diagnosis)		Without coma (secondary diagnosis)		All hospitalizations	
Total		33.130,77 €		143.639,95 €		1.124.686,57 €		3.865.837,39 €		5.167.294,68 €	
average		2.366,48 €		7.560,00 €		1.575,19 €		4.319,37 €		3.146,95 €	
median		1.902,90 €		3.905,61 €		993,91 €		2.057,89 €		1.527,45 €	
		average	**median**	**average**	**median**	**average**	**median**	**average**	**median**	**average**	**median**
average and median cost price per age-group	*0-9*	848,40 €	848,40 €	830,15 €	830,15 €	1.117,50 €	935,23 €	1.541,71 €	1.473,92 €	1.210,76 €	966,06 €
	10-19	1.336,17 €	1.336,17 €	0,00 €	0,00 €	1.148,78 €	878,53 €	5.389,29 €	1.497,38 €	1.933,37 €	967,15 €
	20-29	0,00 €	0,00 €	2.296,98 €	2.296,98 €	1.413,68 €	1.065,01 €	3.949,41 €	1.657,52 €	2.330,68 €	1.203,71 €
	30-39	2.217,70 €	2.217,70 €	2.232,16 €	2.232,16 €	1.332,37 €	1.025,62 €	3.480,80 €	1.450,20 €	2.408,71 €	1.256,15 €
	40-49	2.651,55 €	2.390,84 €	3.483,78 €	3.483,78 €	1.569,83 €	949,27 €	3.758,38 €	1.628,04 €	2.846,70 €	1.366,88 €
	50-59	2.546,46 €	1.755,33 €	5.442,57 €	5.361,05 €	2.566,66 €	1.169,19 €	4.562,84 €	1.991,76 €	4.107,31 €	1.878,29 €
	60-69	0,00 €	0,00 €	5.234,79 €	5.234,79 €	3.748,34 €	1.451,46 €	3.893,85 €	2.569,08 €	3.876,04 €	2.285,45 €
	70-79	2.859,38 €	2.859,38 €	21.032,24 €	7.957,40 €	2.315,74 €	1.181,81 €	4.529,64 €	3.500,76 €	4.662,09 €	3.228,81 €
	80-89	0,00 €	0,00 €	1.270,22 €	1.270,22 €	5.020,02 €	2.360,62 €	7.481,44 €	4.445,96 €	7.131,15 €	3.693,54 €
	90-105	0,00 €	0,00 €	0,00 €	0,00 €	0,00 €	0,00 €	5.365,91 €	2.235,94 €	5.365,91 €	2.235,94 €
average and median cost-price per region	*Flanders*	2.449,54 €	1.522,23 €	5.006,93 €	4.328,87 €	1.522,61 €	981,86 €	4.643,09 €	2.134,90 €	2.966,14 €	1.425,01 €
	Wallonia	1.932,17 €	2.061,50 €	3.670,50 €	2.332,72 €	1.853,36 €	998,58 €	3.868,86 €	1.944,96 €	3.248,17 €	1.658,68 €
	Brussels	2.924,23 €	1.805,99 €	33.270,35 €	33.270,35 €	1.311,38 €	1.107,12 €	4.464,20 €	2.228,79 €	3.219,92 €	1.536,77 €
average and median costprice per nationality	*Belgian*	2.610,62 €	2.030,65 €	4.231,20 €	3.694,69 €	1.606,21 €	987,98 €	4.177,01 €	1.948,88 €	3.024,30 €	1.468,03 €
	EU-inhabitant	467,18 €	458,50 €	36.854,27 €	36.854,27 €	1.792,02 €	1.775,19 €	3.713,66 €	2.063,44 €	4.347,18 €	2.033,81 €
	Non-EU	1.294,71 €	1.294,71 €	2.232,16 €	2.232,16 €	1.310,69 €	1.032,06 €	5.108,23 €	2.618,46 €	3.384,57 €	1.658,68 €

[14] PTCosts brought to 2004 price levels by the CPI for hospital services available on TUhttp://epp.eurostat.ec.europa.eu/portal/page?_pageid=2714,1,2714_61582070&_dad=portal&_schema=PORTALUT
The year 2000 was not available and has been extrapolated from the available years.

Table 23: Hepatitis A encoding frequencies per age group per region

	Coma (primary diagnosis)						Coma (secondary diagnosis)						Without coma (primary diagnosis)						Without coma (secondary diagnosis)					
Age	**Vl**		**Wal**		**Bxl**		**Vl**		**Wal**		**Bxl**		**Vl**		**Wal**		**Bxl**		**Vl**		**Wal**		**Bxl**	
	Nr.	*%*	*Nr.*	*%*	*Nr.*	*%*	*Nr.*	*%*	*Nr.*	*%*	*Nr.*	*%*	*Nr.*	*%*	*Nr.*	*%*	*Nr.*	*%*	*Nr.*	*%*	*Nr.*	*%*	*Nr.*	*%*
0-9	1	14,3	0	0	0	0,0	0	0,0	2	28,6	0	0,0	83	18,2	40	19,5	25	20,5	17	4,3	19	4,1	13	9,1
10-19	0	0,0	0	0	3	50,0	0	0,0	0	0,0	1	16,7	90	19,7	39	19,0	37	30,3	16	4,1	14	3,1	5	3,5
20-29	1	14,3	0	0	0	0,0	1	7,7	0	0,0	1	16,7	72	15,8	37	18,0	23	18,9	36	9,2	34	7,4	14	9,8
30-39	0	0,0	2	40	0	0,0	0	0,0	1	14,3	1	16,7	78	17,1	36	17,6	21	17,2	54	13,7	68	14,8	16	11,2
40-49	1	14,3	2	40	1	16,7	1	7,7	0	0,0	0	0,0	54	11,8	24	11,7	8	6,6	47	12,0	62	13,5	10	7,0
50-59	2	28,6	1	20	2	33,3	5	38,5	2	28,6	0	0,0	31	6,8	12	5,9	4	3,3	60	15,3	75	16,3	17	11,9
60-69	0	0,0	0	0	0	0,0	2	15,4	0	0,0	2	33,3	30	6,6	11	5,4	1	0,8	53	13,5	70	15,3	22	15,4
70-79	2	28,6	0	0	0	0,0	4	30,8	1	14,3	1	16,7	12	2,6	4	2,0	2	1,6	75	19,1	80	17,4	24	16,8
80-89	0	0,0	0	0	0	0,0	0	0,0	1	14,3	0	0,0	7	1,5	2	1,0	1	0,8	33	8,4	34	7,4	18	12,6
90-105	0	0,0	0	0	0	0,0	0	0,0	0	0,0	0	0,0	0	0,0	0	0,0	0	0,0	2	0,5	3	0,7	4	2,8

Table 23 specifies for each age group the Hepatitis A encoding frequencies per region. Most of the hospitalizations with coma are for older age groups, although there are 3 coma patients in the youngest age group.

2.2.4.2 Hepatitis A focused analyses (excluding irrelevant codes)

The former analysis had its focus on a rough classification of HAV cases. All patients with code of diagnosis '0700' or '0701' were considered as relevant, irrespective of other (secondary or primary) diagnostic codes for the same patient. Although such a rough classification is useful to paint the landscape, a more profound analysis is required to check its validity.

In view of this, we also made a more thorough analysis to obtain a more specific estimate of the costs attributable to HAV, based on a subsample of patients, through exclusion of irrelevant diagnostic fields. In the following sections more details are given about this more focused analysis.

Exclusion criteria

The following cascading exclusions left us with a smaller but more representative sample of hospital admissions in which non coma hepatitis A infection played a major part. (see Table 24).

First, for 201 hospitalizations there was no correct linkage between the 'Minimal Clinical Data' (MKG) and their billing counterpart, the 'Minimal Financial Data' (MFG). Also patients with more than one hepatitis A coded admission were excluded. Patients in 'severity index' 0, 3 or 4 were also removed. Severity 0 is considered unreliable, since it belongs to the so called 'waste basket' APrDRGs (955TPTP15PTPT an 956) and severity indices 3 ('major') and 4 ('extreme') indicate important secondary diagnoses, inducing non hepatitis A related costs. In order not to distort the analysis they also need to be excluded. Ten of the remaining hospital stays were hospitalizations for Hepatitis A with coma (either based on code 0700, either separatively coded as 5722) and they were left out of the sample as well since their costs are calculated separately, based on individual examinations of these cases. Hepatitis A in secondary diagnosis is considered a confounder since the costs will mainly reflect the treatment of the primary disorder (551 more exclusions). There were yet another 34 stays with other non-related hepatobiliary diagnoses (such as Alcoholic hepatitis or liver transplant complications - see Table 25). Another 118 stays incurred other costs for irrelevant cost-interfering co-morbidities (Table 26). Furthermore there were 96 stays with unrelated treatments (Table 27) and 2 patients on a chronic ward. A further 57 stays had non related pharmacological expenditures (Table 28) and one patient had a stay categorized in APrDRG 422 (treatment for hypovolemia and electrolyte disorders). In order to obtain a reliable sample we had to exclude all these admissions. These exclusions left us with a subsample of 300 patients, who were most likely treated in hospital specifically for hepatitis A illness.

[15] APrDRG 955 = principal diagnosis invalid as discharge diagnosis and APrDRG 956 = ungroupable stays

Table 24: Exclusion counts

		Starting stays	1.843
Exclusion	**Specification**	**Excluded stays**	**Remaining**
1	201 non linked stays got no billing records	-201	1.642
2	69 patients got > 1 stay with hep A code (same or other hospital) = 153 stays	-153	1.489
3	320 stays / patients in severity 0 (waste basket APrDRGs), 3 or 4	-320	1.169
4	10 stays / patients got hepatitis A with coma (9 in primary diagnosis; 1 in secondary diagnosis)	-10	1.159
5	551 stays / patients got only ICD-9-CM code '0701' as secondary diagnosis	-551	608
6	34 stays / patients got other non-related hepatobiliary diagnoses	-34	574
7	118 stays / patients got other cost interfering co-morbidity	-118	456
8	2 stays / patients in chronical (Sp) ward	-2	454
9	96 stay / patient got non related prestations	-96	358
10	57 stay / patient got non related pharmacological expenditures	-57	301
11	1 stay / patient not in APrDRG 422	-1	300
	Total exclusions	**-1.543**	
	Final inclusions		**300**

Table 25: Non related hepatobiliary and pancreatic diagnoses

Category	Coding frequency
Other viral or protozoal hepatitis (B,C,D,…), acute or chronic	229
Cirrhosis	104
Pancreatic disorders (pancreatitis, cysts, neoplasm,..)	65
Biliairy disorders	52
Hepatic malignancy	38
Other specified disorders of biliary tract	26
Pregnancy related	14
Alcoholic hepatitis	10
Liver transplant complications	10
Liver abces	4
Congenital hepatobiliary disorders	2
Liver trauma	1

Table 26: Other non-related co-morbidity

Category	Stay frequency
Other GI & abdominal	35
Neuropsychiatry	20
Cardiovascular	18
Other infections & zoönoses	17
Hematology	16
Respiratory diseases	8
Endocrinology	6
Gynaecology & obstetrics	5
Urology	5
Orthopaedics	3
Auto-immune diseases	1
Neonatology	1

Table 27: Unrelated treatments

Category	Billing frequency
Neuropsychiatry	293
Oftalmology	210
Orthopaedics	191
Obstetrical & operative assistance	164
Abdominal surgery	122
Otorhinolaryngology	103
Urology	51
Percutaneous interventions	51
Transplantations	36
Thoracic surgery	34
Gynecology- obstetrics	34
Radiotherapy	30
General surgery	27
Genetic counseling	22
Plastic & recinstructive surgery	21
Dentistry	20
Vascular surgery	16
Neurosurgery	14
Stomatology	14
Dialysis	9
Dermato-venereology	4

Table 28: Unrelated phamacology per ATC316 category

ATC3	ATC3 label	Stay frequency
A03B	Belladonna and derivatives, plain	42
B01A	Antithrombotic agents	37
C07A	Beta blocking agents	17
N06A	Antidepressants	15
C10A	Lipid modifying agents, plain	15
R03A	Adrenergics, inhalants	13
R03B	Other drugs for obstructive airway diseases, inhalants	13
A10A	Insulins and analogues	13
R05C	Expectorants, excl. combinations with cough suppressants	13
C09A	Ace inhibitors, plain	11
C01D	Vasodilators used in cardiac diseases	10
H02A	Corticosteroids for systemic use, plain	10
N03A	Antiepileptics	9
A10B	Oral blood glucose lowering drugs	9
N05A	Antipsychotics	7
C08C	Selective calcium channel blockers with mainly vascular effects	7
J05A	Direct acting antivirals	6
H03A	Thyroid preparations	5
J02A	Antimycotics for systemic use	5
M01A	Anti-inflammatory and antirheumatic products, non-steroids	5
J04A	Drugs for treatment of tuberculosis	3
J01A	Tetracyclines	3
C02A	Antiadrenergic agents, centrally acting	3
A05A	Bile therapy	3
D01A	Antifungals for topical use	3

16 Anatomical Therapeutic Chemical Classification System

V07A	All other non-therapeutic products	3
M03A	Muscle relaxants, peripherally acting agents	3
S01C	Anti-inflammatory agents and anti-infectives in combination	2
A01A	Stomatological preparations	2
P01A	Agents against amoebiasis and other protozoal diseases	2
S03C	Corticosteroids and anti-infectives in combination	2
G01A	Antiinfectives and antiseptics, excl. combinations with corticosteroids	2
S03A	Anti-infectives	2
G03C	Estrogens	2
R03D	Other systemic drugs for obstructive airway diseases	2
C08D	Selective calcium channel blockers with direct cardiac effects	2
M04A	Antigout preparations	2
J01E	Sulfonamides and trimethoprim	2
A07E	Intestinal anti-inflammatory agents	1
A07A	Intestinal anti-infectives	1
C01A	Cardiac glycosides	1
D06B	Chemotherapeutics for topical use	1
B02B	Vitamin K and other hemostatics	1
C01B	Antiarrhythmics, class I and I-II	1
H01B	Posterior pituitary lobe hormones	1
G04C	Drugs used in benign prostatic hypertrophy	1
G04B	Other urologicals, incl. antispasmodics	1
C03E	Diuretics and potassium-sparing agents in combination	1
C07B	Beta blocking agents and thiazides	1
C07F	Beta blocking agents and other antihypertensives	1
B02A	Antifibrinolytics	1

Cost Calculations

Cost calculations were performed by adhering to the following principles:

First, in these analyses only costs reimbursed by the 'National Institute for Sickness and Disability Insurance' (NISDI = RIZIV/INAMI) were considered (as these are the only ones readily available from the data). Second, the costs should only reflect costs attributable to hepatitis A by a maximal exclusion of non hepatitis A related costs. Finally, due to flat rate charging in the fields of clinical biology (partially) and hospital care (since july 2002), these costs cannot be obtained directly from the data, but are estimated by indirect extrapolations.

Costs of clinical biology

As an exception to all other costs in MFD records, those for clinical biology are recorded by aggregation in 10 major subgroups (**Table 29**). However, this aggregation concerns only the fraction 'à l'acte'.

Table 29: Subgroups in clinical biology billings 'à l'acte'

Subgroup	Description
01	Blood chemistry
02	Hormonology
03	Toxicology
04	Therapeutic monitoring
05	Microbiology
06	Infectious serology
07	Hematology
08	Coagulation and hemostasis
09	Immuno-hematology and non-infectious serology
10	In vitro fertilisation

Indeed, only a fraction of the clinical biology claims is remunerated 'à l'acte', each with a proper billing code. On the other hand, a vast amount is disbursed through a system of fixed lump sums: one per admission and one, hospital specific, per day of in-hospital stay. Lump sum costs are booked irrespective of actual biology consumption and are also adjusted in case of overspending on the allocated budget.

Hence, the costs of clinical biology registered in the MKG-data do not reflect the true costs and consequently they cannot be simply added to the other costs. Therefore we need to calculate the true costs in an indirect way. For each treatment on average 20% of the costs is accounted 'à l'acte' so by multiplying the costs per act with five, an approximation of the true costs is obtained.

The multiplication factor (×5) was derived from a comparison of national in hospital clinical biology expenditures per year form 1995 to 2006 (see table 30).

Table 30: NISDI in-hospital clinical biology expenditures 1995 - 2006[17]

Year	Costs clinical biology 'à l'acte'	Forfait for clinical biology	Perc of forfait
1995	52.735.410 €	204.244.204 €	21%
1996	56.957.854 €	216.973.304 €	21%
1997	55.011.955 €	198.764.968 €	22%
1998	59.132.467 €	231.936.009 €	20%
1999	61.273.011 €	258.885.572 €	19%
2000	64.637.340 €	280.800.944 €	19%
2001	68.785.284 €	281.706.962 €	20%
2002	70.278.789 €	317.100.190 €	18%
2003	74.596.511 €	318.904.270 €	19%
2004	77.004.632 €	305.348.186 €	20%
2005	79.063.895 €	345.578.702 €	19%
2006	80.409.117 €	314.331.842 €	20%
All years	**799.886.265 €**	**3.274.575.155 €**	**20%**

Included costs of clinical biology are presented in table 31:

Table 31: Included costs of clinical biology

Subgroup	Description	Stays	NISDI cost
1	Blood chemistry	289	6.552,39 €
6	Infectious serology	237	3.290,89 €
5	Microbiology	162	1.147,03 €
7	Hematology	267	902,04 €
8	Coagulation and hemostasis	210	664,76 €
9	Immuno-hematology and non-infectious serology	53	284,40 €
2	Hormonology	71	234,74 €
3	Toxicology	7	93,34 €
4	Therapeutic monitoring	9	29,00 €

Costs of hospital care

The costs due to hospital care of patients are also difficult to obtain. Before 07/2002 there was a full remuneration on billing codes. Due to changes in legislation however the accounting system changed. Eighty percent (80%) of the allocated costs are disbursed through a separate system of hospital budget allocations: BFM/BMF (Budget Financiële Middelen van de zorginstellingen/ Budget des Moyens Financiers des institutions de soin) and those allocations are not transmitted with the MFD records.

Ten percent of the costs is a disbursed through a hospital specific lump sum per admission, irrespective of the length of stay, and another 10% is through a lump sum per day of stay, variable according to the type of ward the patient is staying in. By multiplying the lump sums per day of stay for relevant billing codes (acute and chronic, non palliative hospital wards) by the LOS and an additional factor 10, an approximation of the true costs for hospital care can be made.

17 Source: NISDI, doc N

This multiplication factor is dependent on the field of treatment. For example, for palliative care, psychiatry and burns centres this factor is 5, since no lump sum per admission is dued in those cases, meaning that 20% of allocated costs are disbursed through the lump sum per day of stay (see Table 32)

Table 32: NISDI lump sum billing codes for hospital care (since July 2005)

Lump sum per	Billing code	Applies to	Multiplication factor
admission	768003	Acute hospital departments	0
admission	768084	Chronic departments (non palliative) (rescinded starting 01/07/2005)	0
day of stay	768025	Acute hospital departments	10
day of stay	768106	Chronic departments (non palliative)	10
day of stay	768143	Palliative care	5
day of stay	768121	Psychiatry	5
day of stay	768165	Burns centres	5

Costs of pharmaceuticals

As stated higher only hepatitis A related costs for pharmaceuticals were included. Table 33 summarizes included costs per ATC2-category (Anatomical Therapeutic Chemical Classification SystemTPTP[18]PTPT).

Table 33: Included pharmaceutical costs per ATC2-category

ATC2	ATC2 label	Stays	NISDI cost
B05	Blood substitutes and perfusion solutions	236	3.832 €
J01	Antibacterials for systemic use	9	678 €
V08	Contrast media	12	527 €
A02	Drugs for acid related disorders	47	384 €
N02	Analgesics	56	320 €
A03	Drugs for functional gastrointestinal disorders	85	150 €
R06	Antihistamines for systemic use	14	21 €
A06	Laxatives	1	8 €

Fee costs

Not all medical fees were included: costs of manifestly unrelated treatments were excluded (see table 27). Included medical fees are summarized in table 34

Table 34: Included medical fees

N-group label	Stays	NISDI cost
Surveillance fees	300	33.200 €
Röntgendiagnosis	300	28.092 €
N / WE supplements	81	6.037 €
Paediatrics	27	1.427 €
ECG & related	60	1.075 €
Reanimation & IC	6	410 €
Gastro-entereology	4	402 €
Other, general	7	460 €

After these adjustments we obtain a specific sample of HAV hospitalizations in which we can accept that all the costs are reasonably linked to Hepatitis A. In the remaining sample, the accepted co-morbidities can be categorized as "general symptoms", "acidosis, plasmaprotein & electrolyte disturbancies", "nicotine, alcohol & other abuses" and "common biology abnormalities"

18 The Anatomical Therapeutic Chemical Classification System is used for the classification of drugs. It is controlled by the WHO Collaborating Centre for Drug Statistics Methodology, and was first published in 1976.The classification system divides drugs into different groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics

Results of specific subgroup analysis

Age

In this sample we find that the median age is 17 and the average 20.7. Figure 16 shows there seems to be a slight (non-significant) increase in average age over the years. In 2000 the median age was 13. From 2001-2003 the median was at 17 years of age and in 2004 the median rose to 25 years. This rise in age seems to be consistent with the finding that the average admitted case presents with a broader and more severe array of symptoms (due to a federal Health Care policy favouring day care admission over classical hospitalization).

Figure 16 Sub group analysis: Age distribution of hospitalized HAV patients per year (box plots)

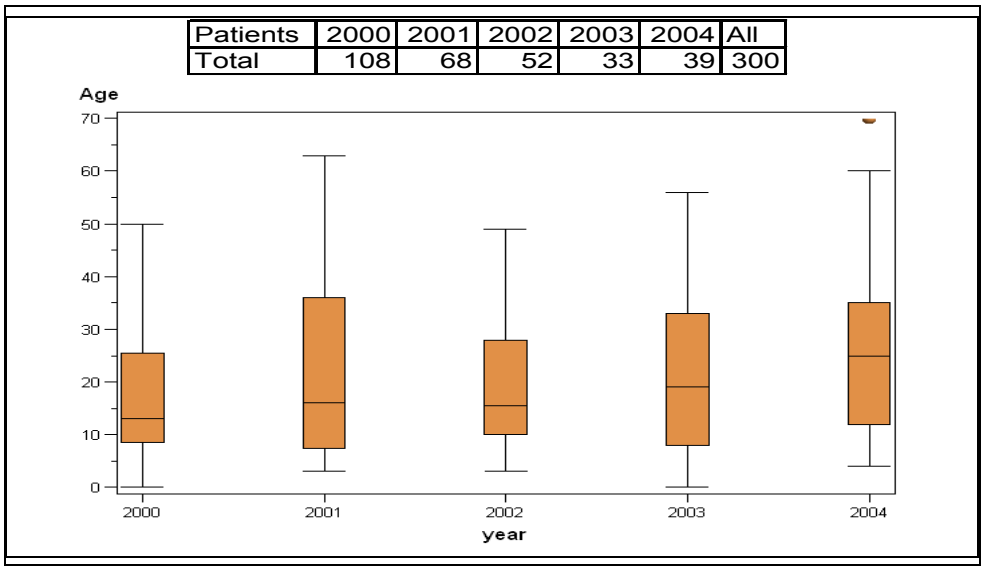


Table 35: Sub group analysis: Age distribution of hospitalized HAV patients per year

Year	2000	2001	2002	2003	2004	All
N	108	68	52	33	39	300
Mean	17.76	22.61	19.65	21.57	26.28	20.72
Median	13	16	15.5	19	25	17

Length of stay

The average length of stay in the hospital due to Hepatitis A in our subgroup analysis is 4.01 days while the median is 3 days. During the five years under study the length of stay is distributed equally, although there are some outliers.

Figure 17: Subgroup analysis: Distribution of length of stay of hospitalized patients per year (box plots)

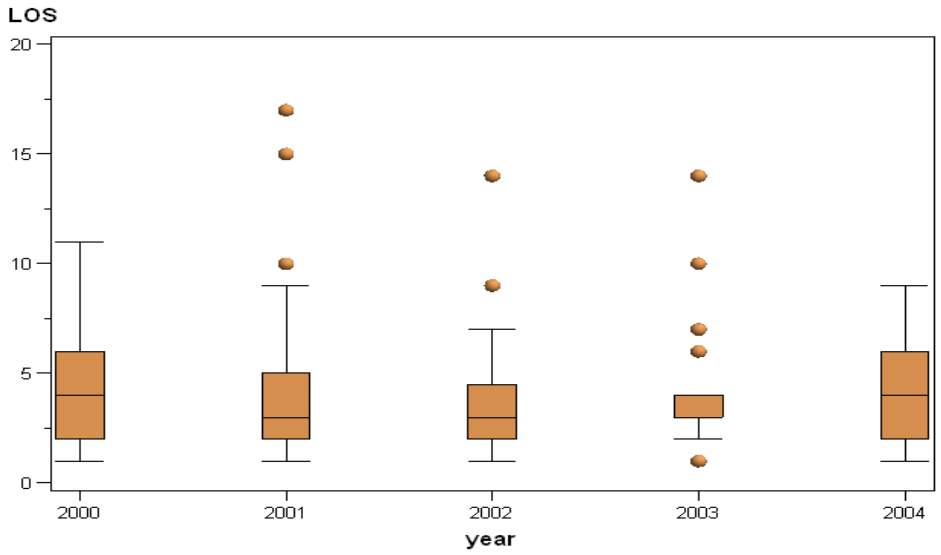


Table 36: Subgroup analysis: length of stay of hospitalized patients per year

Year	2000	2001	2002	2003	2004	All
N	108	68	52	33	39	300
Mean LOS	4.12	4.01	3.69	4.24	3.92	4.01
Median LOS	4	3	3	3	4	3

The cost of a hospitalization

Now that we have a representative sample with – to the best of abilities – hepatitis A treatment restricted costs, we can estimate a specific cost to the 'Sickness and Invalidity Insurance' of a hospitalization due to hepatitis A. In our clean sample, the only variable with a significant influence on the costs is age. There is no significant time trend.

The mean cost of a hospitalization for HAV is €1,401, the median is €1,262, and the range is € 316 – €4,182.

Figure 18: Sub group analysis: Distribution of hospitalization costs (all years, all ages)

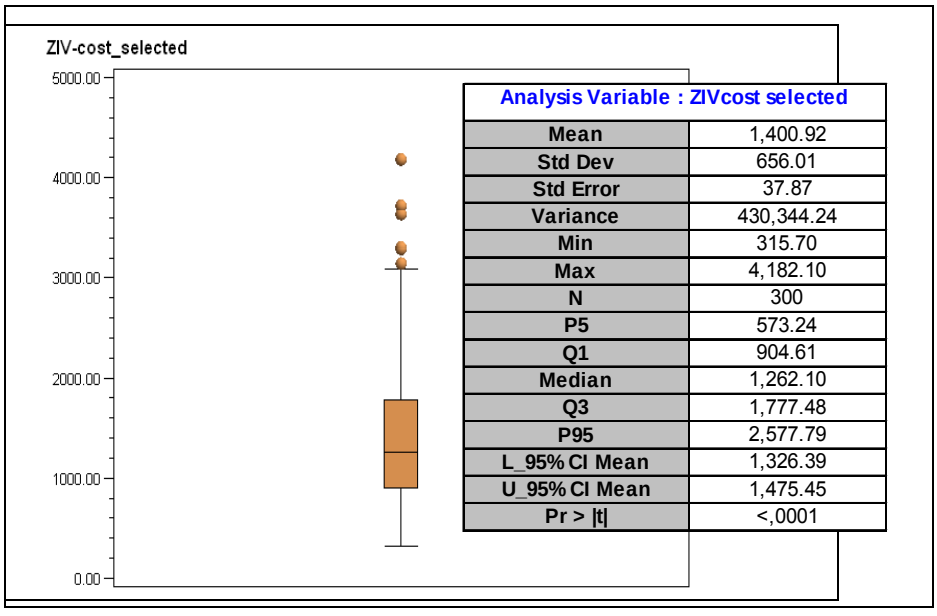


Table 37 presents the cost distribution for two age groups: < 15 years and age 15 or more, with the latter age group incurring higher costs (median cost € 1,047 and €1,446, respectively).

Table 37: cost distributions for patients hospitalised with hepatitis A, <15 years of age and age 15 or more, based on subgroup sample (n=300)

	Age < 15	Age 15 or more
Inputdata (N)	140	160
median	€ 1,047.20	€ 1,446.58
mean	€ 1,256.50	€ 1,527.29
min	€ 315.70	€ 371.41
max	€ 3,034.13	€ 4,182.10
St. Dev.	€ 556.7	€ 707.5
95% interval	€ 495- € 2,633	€ 480- € 3,290
Distribution	Loglogistic	Weibull
Median	€ 1,130.55	€ 1,417.01
Mean	€ 1,279.25	€ 1,527.05
min	€ 152	€ 344
max	+Infinity	+ Infinity
St. dev.	722.7	707.1
95% interval	€491- € 2,974	€ 501- € 3,174

Figure 19: Distribution of hospitalization costs per year (box plots)

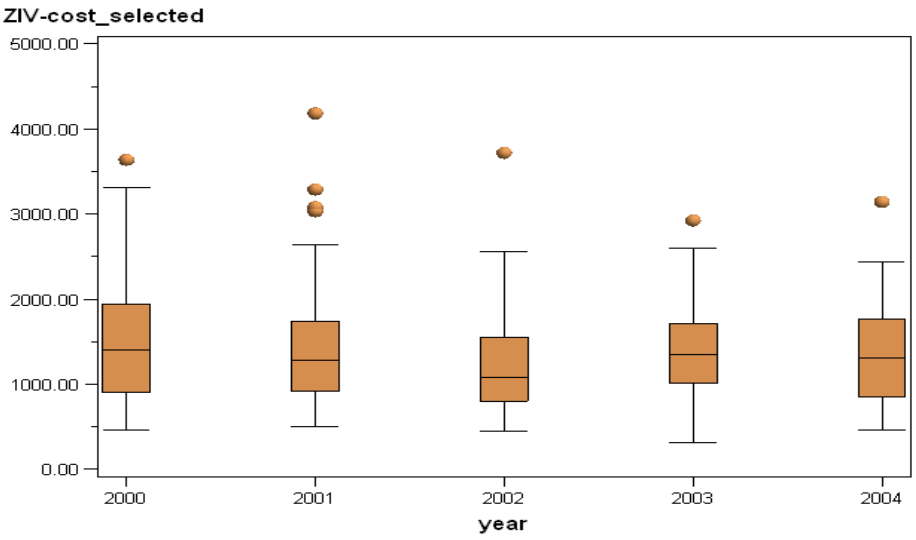


Table 38: Subgroup analysis: hospitalization costs per year

Year	2000	2001	2002	2003	2004	All
N	108	68	52	33	39	300
Mean	€1,452.25	€1,466.39	€1,245.39	€1,398.47	€1,354.06	€1400,92
Median	€1,397.54	€1,285.10	€1,078.45	€1,354.34	€1,314.52	€1,262.09

Comparing the subgroup with the overall analysis

Now we can compare the findings of the sub group analysis with the larger but less specific (and thus less reliable) sample.

Over the time period studied, there were 711 Hepatitis A admissions without coma as primary diagnosis in the coupled MKG-MFG database. An analysis of this group provides similar information as the more specific subgroup analysis described above.

If we compare the findings of the specific subgroup analysis with our most basic group of all hospitalizations with HAV in a diagnostic field, we see that the average is higher: € 1,897 vs. 1400 €. The median gives a less distorted image: € 1,479 in the basic sample against € 1,262 for the clean sample. This is illustrated in figure 20 and figure 21 for the length of stay per admission and the hospitalization costs per admission, respectively. These compare fairly well with the figures in the previous section.

Figure 20: Distribution of length of stay of hospitalized patients per year

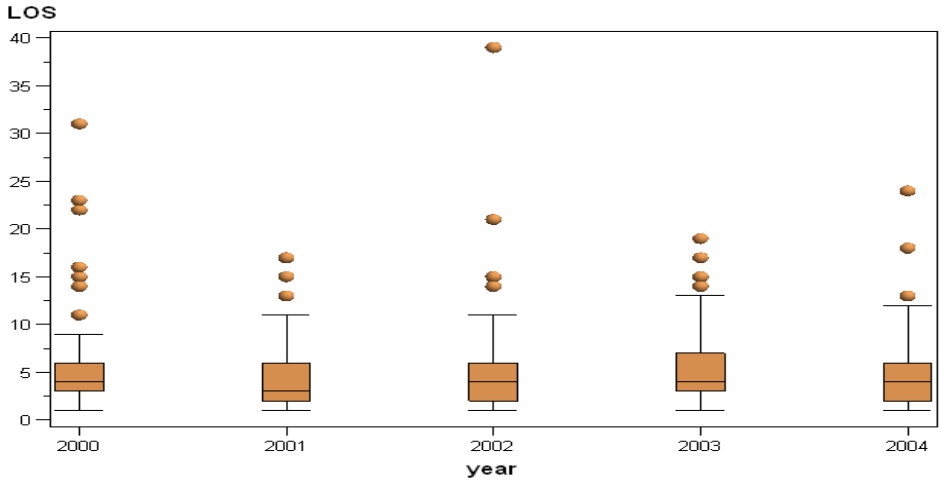


Table 39: Distribution of length of stay of hospitalized patients per year

Year	2000	2001	2002	2003	2004	All
N	201	136	133	99	142	711
Mean	5.4	5.1	5.3	5.1	5.3	5.3
Median	4	3	4	4.	4	4

Table 40: Cost distributions for patients hospitalised with hepatitis A without coma in primary diagnosis, <15 years of age and age 15 or more , based on total sample (n=711)

	Age < 15	Age 15 or more
Inputdata (N)	224	487
median	€ 1,187	€1,671
mean	€1,341	€2,153
min	€304	€331
max	€7,526	€31,282
St. Dev.	€756	€2,516
95% interval	€490-€2,920	€580-€5,910
Distribution	Loglogistic	Loglogistic
Median	€1,174	€1,644
Mean	€1,349	€2071
min	€154	€237
max	+ Infinity	+ Infinity
St. dev.	€832,4	€2071
95% interval	€490-€3,270	€570-€6,120

2.2.5 A prospective survey of Non-hospital costs, Health Related Quality of life (HRQOL) impact and work loss related to Hepatitis A

2.2.5.1 Study design

In order to estimate the consequences of various manifestations of clinical hepatitis A disease on medical consumption and Health Related Quality of life (HRQOL), we developed 3 different questionnaires in both the Dutch and French versions, which were administered prospectively at different points in time to patients recently diagnosed with hepatitis A.

Questionnaires were presented by the health inspection prospectively to all new cases reported to the health inspection services in Flanders. The Wallonian and the Brussels health inspection services (besides "Vlaams Brabant"/"Flemish Brabant") were invited to participate, but preferred not to due to the lack of sufficient personnel). These questionnaires included general information on resource consumption and clinical disease (see appendix A), as well as standardised HRQOL surveys, namely the Euroqol questionnaire, EQ-5D (administered shortly after reporting) including a rating scale (RS) and general background information, and the SF-12, administered after symptoms have passed. The instructions for the practical organisation of these surveys are also given in appendix A. These questionnaires were sent to hepatitis A cases notified to the provincial health inspection services. Each new patient thus received 3 lists of questions.

More specifically,

1. Questionnaire A, which included the EQ-5D with the RS, was sent to patients immediately after notification.
2. Questionnaires B1 and B2 were sent three to four weeks later. In B1 information is gathered on the experienced symptoms and consumption of medical care over the entire episode. B2 consisted of the internationally widely used SF-12v2 health survey to gauge the QoL impact over the entire past period of illness.

2.2.5.2 Survey results

Between 1st February and 30th September 2008 we received 54 completed questionnaires A, 52 completed questionnaires B1 and 50 completed questionnaires B2. For 44 patients we received the complete set of three linked surveys. The overall response rate seemed acceptable at 39%, though it appears that more urbanised provinces suffered from an overall lower response ratio.

Table 41: Responses to prospective survey by province

	Antwerp	Flemish-Brabant	Limburg	West-Flanders	East-Flanders	Total
Full packages sent	51	16	29	6	10	112
Surveys A received (response %)	19 (37%)	4 (25%)	22 (76%)	4 (67%)	5 (50%)	48%
Full packages received (response %)	11 (22%)	3 (19%)	21 (72%)	4 (67%)	5 (50%)	44 (39%)

In this section we discuss the results of the first two surveys: questionnaire A and B1 (see appendix).

Table 42 shows the number of surveys according to the respondents' age and hospitalisation status. For 8 out of 52 respondents of questionnaire B1, specific information on age was lacking, but from other information in the questionnaire one respondent was known to be an adult and another was known to be a child. Therefore only 6 respondents could not be categorised in either of the two broad age categories we considered: < 15 years and ≥ 15 years.

Only 1 of the responding HAV patients < 15 years was hospitalized, as were 8 responding HAV patients ≥ 15 years.

Table 42: Number of surveys by age and hospitalisation status

Age group	Non-hospitalised		Hospitalised		Total*	
	A	B I	A	B I	A	B I
< 15 years	20	21	1	1	26	22
≥ 15 years	16	16	5	8	28	24
Unspecified[a].	0	6	0	0	0	6
Total	36	43	6	9	54	52

*The totals do not always add up from separate group counts, because for not all responders hospitalisation status was known with certainty

PPa PPUnspecified: Age was not specified, and broad age group could not be determined from other information in the survey

The average and the median age of the sample was respectively 25.15 and 23 years of age, but within the two broad age groups the average and median was 7 and 6 for the children, 42.6 and 40 for the adults. The average age of a hospitalized patient was 45 (median 40). When we examine the level of schooling of the older agegroup more than half of the patients followed higher education. Eighty percent stated that they were full-time employed. These two findings at first sight do not indicate that HAV infection is positively correlated to lower socio-economic status. Eighty-nine percent of the responding adults had no experience as a healthcare worker. A small minority indicated that they were smokers or ex-smokers: 18 percent in the adult age group. The answers about smoking for the group below 15 are not reliable since possibly parents filled in the list for their child and noted whether they were smokers or not.

Table 43: Main survey results relating to questionnaire A (see appendix A)

		All patients	< 15 years, total	≥ 15 years, total	< 15 years, non-hospitalised	≥ 15 years non-hospitalised	≥ 15 years hospitalised
Number of respondents [a]		54	26	28	20	16	5
Age (years)	Mean	25.1	7.0	42.6	6.8	39.3	45.0
	Median	23	6	40	6	39	40
sex	Male	53%	58%	48%	56%	44%	60%
EQ-5D score [b]	Mean	0.6091	0.6958	0.5357	0.6620	0.5633	0.3108
	Median	0.6607	0.7333	0.5300	0.7333	0.5300	0.2892
	Standard deviation	0.2976	0.2842	0.2941	0.2863	0.2732	0.2714
Visual Analogue Scale (VAS), raw score [c]	Mean	65.4	74.8	56.0	71.1	59.3	47.3
	Median	67.0	80.0	60.0	80.0	60.0	47.5
	Standard deviation	23.3	23.9	18.9	26.3	19.4	23.0
Visual Analogue Scale (VAS), rescaled	Mean	0.580	0.693	0.466	0.648	0.505	0.359
	Median	0.633	0.778	0.556	0.778	0.556	0.417
Professional status	Full time	48%	0%	80%	0%	81%	89%
	Part time	12%	0%	8%	0%	12%	11%
	retired	2%	0%	4%	0%	0%	0%
	housework	5%	7%	4%	11%	0%	0%
	student	31%	86%	4%	89%	6%	0%
	in search of work	2%	7%	0%	0%	0%	0%
	other	0%	0%	0%	0%	0%	0%
Health care worker experience	Yes	7%	0%	12%	0%	12%	0%
Experience with severe disease	yourself	13%	14%	12%	19%	12%	0%
	family members	33%	12%	50%	14%	60%	25%
	by helping others	3%	0%	6%	0%	8%	0%
Current disease experience relative to onset of symptoms	Worse than at the start	6%	0%	11%	0%	6%	40%
	Better than at the start	34%	16%	50%	22%	50%	40%
	Not better nor worse than at the start	9%	8%	11%	6%	12.5%	0%
	Almost over	26%	36%	18%	44%	19%	20%
	Completely over	17%	28%	7%	16%	6%	0%
	I have never felt sick at all	8%	12%	4%	11%	6%	0%

a) Numbers do not add up, because hospitalisation status was recorded only in the second questionnaire B1, and not all responders to questionnaire A responded to questionnaire B1
b) EQ-5D score based on Flemish valuation set (KCE reports 78C "Guidelines for pharmacoeconomic evaluation in Belgium"), in total 6 out of 54 responders provided no (n=5) or an invalid score (n=1)
c) score directly obtained from respondents jointly with their EQ-5D score, in total 4 out of 54 responders did not provide a VAS score

Of 54 responders of the EQ-5D survey, 26 (or 48%) were aged < 15 years and 28 (52%) ≥ 15 years. Of the latter group, 21 responders were definitely not hospitalized, and of the remaining 7 surveys, 5 provided valid EQ-5D scores for hospitalized cases. The mean EQ-5D score was 0.5934, based on the Flemish reference score, and the median score was 0.6607. When patients were asked to indicate their health status on a visual analogue scale (with the maximum score of 100 corresponding to the best health state imaginable), the results were similar, with a mean of 65.4 and a median 67, which was made comparable by rescaling based on the valuation of the death state to 0.58 and 0.63, respectively. As shown in **Table 43** the results between EQ-5D and the VAS score concur also for the other subgroups.

The results are consistent with the fact that hepatitis A illness is more severe with increasing age at infection. For children < 15 years of age, the EQ-5D score (mean 0.6957; median 0.7333) was lower than their VAS score (mean 74.76; median 80). However, both of these scores were higher than for patients aged ≥ 15 years (mean 0.5099 and median 0.53 for EQ-5D; mean 56.04 and median 60 for VAS).

At the moment of completing the survey, i.e. more or less a week after the first symptoms had appeared, 77% of the entire sample stated that they were in a better disease state compared to the onset. Seventeen percent even responded that their episode was over, and 8% responded that the disease had always remained asymptomatic. In the group < 15 years of age no one stated that their health was worse than in the beginning of the infection, while this was the case in 11% of the older group. The sum of all cases that was in a better state now than in the beginning, i.e. the sum of the categories “better”, “nearly over”, and “entirely over” is similar in both groups: 80% in the younger and 75% in the older age group. However, in the older group 50 % responded to be “better”, whereas in the younger group 64% responded that it was “nearly over” or “entirely over”. It is noteworthy that the latter responses were provided by proxy, and not by the patients themselves, as was the case in the other age group. Also the fraction of both samples that experienced an asymptomatic course of illness differed in the way we would expect: 12% in the younger group vs. 4% in the older agegroup (though it should be stressed that these results are based on notified cases, which would show a much greater proportion of symptomatic cases than a general sample of infected persons (see section 2.2).

Table 44: Main survey results on symptoms and source of infection (questionnaire B1)

		All patients	< 15 years, total	≥ 15 years, total	≥ 15 years non-hospitalised	≥ 15 years hospitalised
Number of respondents		51	21	23	16	8
Symptoms	Yellow colorisation of skin	75%	62%	91%	94%	86%
	Yellow colorisation of eyes	84%	81%	91%	94%	86%
	Generally tired and listless	86%	76%	96%	94%	100%
	Nausea	67%	67%	65%	56%	88%
	Dark urine	78%	71%	87%	93%	75%
	Diarrhoea	39%	48%	35%	43%	13%
	Pale excrements	63%	62%	65%	69%	63%
	Hardening of the stomach	16%	19%	9%	13%	0%
	Problems with stomach or intestines	61%	71%	57%	69%	25%
	Pain in the chest	14%	10%	22%	31%	0%
	Headache	47%	48%	48%	50%	50%
days ill	mean	19.09	17.00	19.84	18.57	23
	median	18.00	20.00	18.00	14	23
lost days of work	mean	24.1	17.1	30	26.9	40.3
	median	15	15	27	20	44
Any assistance	no one	35%	35%	23%	20%	38%
	a member of the family	63%	65%	73%	73%	63%
	a friend	13%	0%	27%	20%	38%
	professional help	0%	0%	0%	0%	0%
	someone else	0%	0%	0%	0%	0%
paid assistance		0%	0%	0%	0%	0%
lost workdays by others	No	73%	60%	86%	86%	88%
	Yes, on average … days	14.1	13.6	13.3	10	20
	Median	10	7.5	10	10	20
Source of infection	foreign country	19%	17%	26%	31%	5%
	restaurant	13%	0%	26%	25%	9%
	contact with others	35%	44%	22%	19%	14%
	other	52%	0%	4%	0%	5%
Respondent is foodhandler	Yes	6%	5%	9%	6%	13%
Travelling during last 2 months	Yes	24%	20%	8%	37%	71%
Infected persons close to you before your infection	No	58%	50%	71%	73%	71%
Infected persons close to you after your infection	No	61%	52%	71%	60%	86%

Table 45: Main survey results on resource use (questionnaire B1)

		All patients	< 15 years, total	≥ 15 years, total	≥ 15 years non-hospitalised	≥ 15 years hospitalised
GP consults (all)	mean	3	2.3	3.7	3.7	3.6
	median	3	2	3	4	3
GP consults at home	mean	1	0.4	1.6	1.6	1.5
	median	0	0	1	1	1.5
Specialist consults	mean	1.1	1.5	0.6	0.7	0.5
	median	1	1	0	0	0.5
Received medication		27%	20%	36%	40%	25%
blood tests taken	yes	98%	95%	100%	100%	100%
	mean number	3.3	2.2	4.4	2.8	7.6
	median number	3	2	3	3	6.5
echographies	No	66%	90%	45%	53%	0%
	Yes	34%	10%	55%	47%	100%
	Mean number	1.2	1	1.2	1.4	1.1
	Median	1	1	1	1	1
other investigations	No	92%	100%	82%	87%	75%
	Yes	8%	0%	18%	13%	25%
liver transplantation		2%	0%	5%	0%	12%
Emergency service visit		21%	10%	27%	7%	25%
Hospitalisation	Yes	8%	0%	32%	0%	100%
	Mean number of nights if hospitalised	4.75	0	4.75	0	4.75
	Median number of nights if hospitalised	3	0	3	0	3
Vaccine prophylaxis for other people you know	Yes	76%	81%	76%	67%	86%
	mean number of other persons vaccinated	4.2	3.2	5.6	5.7	5.3
	median number of other persons vaccinated	3	4	5.5	6	4.5
Received HAV vaccine prior to infection?	Yes	23%	24%	24%	34%	0%

Questionnaire B1 informs us on specific symptoms of the disease and on the consumption of medical care and other resources. Of the 52 responses, 21 (or 40%) came from respondents under 15 years of age, 23 (or 44%) from patients aged 15 or older and 8 (or 15%) could not be linked to age. Among the older agegroup there were 16 non-hospitalized cases and 7 hospitalized. We also found one hospitalized patient in the group without age that clearly belonged to the adult group. Therefore this patient was also included which left us with 8 prospective surveys from hospitalized cases.

On average, respondents reported 5.7 of the 11 symptoms pre-specified in the questionnaire. Each symptom was experienced by more than 50% of repondents, except for three: pain in the chest (14%), hardening of the stomach (16 %) and diarrhoea (39 %).

The only symptoms hospitalised patients ≥ 15 years reported more frequently than non-hospitalised patients were nausea (88% versus 56%) and general tiredness (100% versus 94%).

Older age proved a more influential determinant of the frequency of symptoms: only the symptoms "diarrhoea" "hardening of the stomach" and "stomach and intestine problems" were reported more often for children than for adults. Symptoms that were similarly divided between both age groups were nausea (67% in the older and 65% in the younger group), pale excrements (62% vs 65%) and headache (both 48%).

The average duration of illness was 19 days (median 18). There seemed to be no marked difference between the age groups in this respect. However the number of lost workdays differed significantly from the number of lost days of school for children: the older age group missed on average 30 days of work (median 27) while the equivalent in the younger group was 17 (median 15). The hospitalized cases were ill for a longer time; they were on average 23 days ill (median 23) and missed on average 40.3 days of work (median 44), which is twice as long as the duration of absence for adults who were not hospitalized.

Sixty-three percent of the respondents were assisted during their illness by a member of the family, 13% by a friend and 35% by no one. None of the respondents declared that he or she paid for assistance. Nonetheless, 27% of those providing assistance lost workdays because of their help (average 14, median 10). This number is again twice as high in the hospitalized group: on average 20 lost workdays by others (median 20).

Patients had on average 3 GP visits of which 1 was a home visit. This is slightly higher in the older than in the younger age group: 3.7 GP visits versus 2.3 GP visits and 0.4 home visits in the younger age group. Specialist consults are markedly more frequent for children (1.5) than adults (0.7). Most patients (73%) do not take any medication for their HAV episode, but adults use more medication than children.

Ninety-eight percent underwent blood tests, on average 3.3 in number, with more than twice as much (7.6) in hospitalised patients.

One in three cases in the entire population had at least one echography taken (average number 1.17, median 1). In the hospitalized group all patients had on average 1 echography. A large majority, 92%, says that no other investigations took place (i.e. X-rays, scannings, etc.).

One adult patient reported having received a liver transplant.

Most cases did not go to the emergency services for their disease (79%). However 75% of the hospitalized cases stated that they consulted the emergency services.

Eighteen percent of the respondents states that he or she was hospitalized. Of all nine hospitalized patients, none were to be found in the younger age group, 7 in the older group and 2 patients with an unknown age. In the older agegroup the average number of hospitalnights was 4.75 (median 3).

Nineteen percent of the cases claims to be infected in a foreign country, 13% in a restaurant and 35% through contact with others.[19] Six percent of the respondents claims to be foodworker. Twenty-four percent has been travelling during the last two months. Nearly half of the cases (42%) had been close to infected persons before infection.

A similar percentage (39%) had infected persons close to him or her after the infection. In 76% of the cases there was precautionary vaccination for people closely related. The average number of vaccines administered to relatives, friends, etc in this group was 4.1 (median 3). Seventy-seven percent says not to be vaccinated before their infection.

[19] Percentages do not add up to 100% due to some multiple responses per patient.

2.2.6 Deaths attributable to Hepatitis A in Belgium

The number of deaths that are attributable to HAV is not directly traceable in existing Belgian databases.

We had access to 2 separate datasets, which allow inferences to be made. First, a list extracted from the MKG database, of all Belgian "in-hospital-deaths" linked to an infection with HAV for the period 2000-2004. Second, a list of death certificates of all people in the Flemish region for whom infection with Hepatitis A or unspecified viral hepatitis was registered as a cause of death during the period 1999-2005.

2.2.6.1 MKG-data (2000-2004)

The MKG-data cover all Belgian hospitalized patients with a diagnosis of hepatitis A, including those who died in hospital. Whereas the different diagnoses for these hospitalized patients are registered for their hospital stay, for those who died in hospital, the main cause of death amongst these different diagnoses is not known with any certainty.

In order to estimate the number of these in-hospital-deaths for HAV, we asked four clinical experts (3 hepatologists, 1 internal medicine) to give their opinion on which patients most probably died because of their hepatitis A infection (i.e. they were asked to focus on whether these patients would have died during their hospitalization if they had not had a hepatitis A infection at that time). Since many of the primary and secondary diagnoses were interlinked (these were often patients with serious co-morbidities), it proved difficult to establish an irrefutable causal link between their hepatitis A infection and their death.

During the period 2000-2004 there were 48 Belgian in-hospital-deaths diagnosed with hepatitis A (amongst other diagnoses). The consulted experts eliminated unanimously 27 deaths as not related to HAV. For the remaining 21 deaths the judgments varied. Of these 21 deaths, 11 were from Flanders, 4 from Wallonia and 6 from the Brussels Capital Region (see **table 46** given below). None of these 21 deaths was unanimously positively attributed to hepatitis A ("YES" in **table 47**). However, 1 death (a 79 year old woman) was considered to be positively due to hepatitis A by two experts, while the other 2 experts did not strongly disagree as they indicated that this person possibly ("MAYBE" in table 49) died due to hepatitis A. A further 3 deaths were unanimously thought to be "MAYBE" due to hepatitis A (all men, aged 42, 74 and 78 years, respectively). About the other deaths, there was more disagreement. Another 58 year old man was thought to have died from hepatitis A according to 2 experts, but not ("NO" in **table 47**) according to a third one, and "MAYBE" according to a fourth expert. These 5 deaths, which can be called probable HAV deaths (according to these data and judgments only) are highlighted in **table 47**.

Table 46: Hospitalizations with a code of hepatitis A, resulting in death

		Coma (Primary diagn)	Coma (secondary diagnosis)	Without coma (primary diagn.)	Without coma (secondary diagn)
total number		3	4	3	38
region	*Flanders*	2	3	1	16
	Wallonia	0	0	0	14
	Brussels	1	1	2	8
Nationality	*unknown*	0	0	2	12
	Belgian	2	3	0	24
	EU-inhabitant	1	1	0	1
	non-EU	0	0	1	1
Age	*0-9*	0	0	0	0
	10-19	0	0	0	1
	20-29	0	0	0	1
	30-39	0	0	1	1
	40-49	0	0	0	1
	50-59	1	1	0	4
	60-69	0	1	0	4
	70-79	2	2	0	11
	80-89	0	0	2	13
	90-105	0	0	0	2

Table 47 gives a general overview of hepatitis A associated hospitalizations ending in death over the period 2000-2004. The majority of these deaths occurred in the older age groups.

Table 47: Year, age, sex, nationality, region and expert judgment of hospitalizations in Belgium with a diagnostic code of hepatitis A and ending in the patient's death according to the National Minimal Clinical Data (MKG/CRM, 2000-2004)

Year	sex	age	Nationality*	Expert 1	Expert 2	Expert 3	Expert 4
Flanders							
2000	F	83	0	NO	MAYBE	MAYBE	MAYBE
2000	F	71	1	NO	MAYBE	MAYBE	MAYBE
2001	F	61	1	MAYBE	NO	NO	NO
2001	M	78	1	MAYBE	NO	MAYBE	NO
2002	F	79	1	MAYBE	YES	MAYBE	YES
2002	M	67	1	MAYBE	NO	MAYBE	MAYBE
2002	M	42	0	MAYBE	MAYBE	MAYBE	MAYBE
2003	M	74	2	MAYBE	MAYBE	MAYBE	MAYBE
2004	M	53	1	NO	NO	NO	MAYBE
2004	M	17	1	MAYBE	MAYBE	NO	NO
2004	M	59	1	MAYBE	NO	NO	MAYBE
Wallonia							
2000	M	81	0	MAYBE	NO	NO	MAYBE
2002	F	83	1	MAYBE	NO	MAYBE	MAYBE
2003	F	78	1	NO	MAYBE	MAYBE	NO
2004	F	87	1	NO	NO	MAYBE	NO
Brussels							
2000	M	58	1	YES(?)	YES	NO	MAYBE
2000	F	87	0	NO	NO	MAYBE	NO
2001	M	78	2	MAYBE	MAYBE	MAYBE	MAYBE
2002	F	37	3	NO	NO	MAYBE	NO
2003	F	82	1	NO	MAYBE	MAYBE	NO
2003	M	81	0	NO	MAYBE	MAYBE	NO

* Nationality 0: unknown; 1: Belgian; 2: Non-Belgian but within the EU, 3: Non-Belgian outside the EU.
NO: Unlikely due to hepatitis A; MAYBE: possibly due to hepatitis A; YES: Likely due to hepatitis A

2.2.6.2 *Death certificates from the Flemish region*

Table 48 presents all Flemish residents who were registered to potentially have died in Flanders or Brussels because of their infection with viral hepatitis A, or unspecified viral hepatitis during the period 1999-2005. Note that for only 9 of these 21 registered deaths, the underlying cause is specifically coded with hepatitis A, while the remainder is coded with unspecified viral hepatitis.

Table 48 : Age, sex, year of death and main ICD 10 codes as indicated on Flemish death certificates including hepatitis A and unspecified viral hepatitis as an underlying cause of death (1999-2005) ; rows in italic shows overlap with MKG data above

year	sex	Age (years)	Registered underlying ("oorspronkelijke") cause of death (ICD 10)*	Direct ("onmiddellijke") cause of death (ICD 10)*	Intermediary (IC) and additional causes (AC) of death
1999	F	80	B15.9	NS	NS
1999	F	90	B19.9	K74.6	NS
1999	M	79	B15.9	NS	NS
1999	M	58	B15.9	NS	NS
2000	M	85	B19.0	R57.0	pneumonia and pulmonary oedema as AC
2000	M	71	B15.9	K72.9	K74.6 as IC
2000	M	78	B19.9	K72.9	Malignant neoplasm of prostate as AC
2000	F	83	B15.9	K76.9	NS
2001	M	56	B19.9	NS	neoplasm as AC
2001	M	72	B19.9	K72.9	acute renal failure as AC
2002	F	76	B19.9	K74.6	septicaemia and s. pneumoniae as AC
2002	F	85	B19.9	NS	Malignant neoplasm of gallbladder as AC
2002	F	78	B15.9	K72.9	NS
2003	M	31	B19.9	A41.9	bronchopneumonia as IC
2003	F	93	B15.9	K74.6	NS
2003	M	74	B15.9	I46.9	Gastrointestinal haemorrhage and coagulation defect as IC and diabetes as AC
2003	M	76	B19.9	I50.9	NS
2004	F	55	B19.9	NS	Portal vein thrombosis, stomach as AC
2005	M	61	B15.9	K72.9	Transplanted organ and tissue status as AC
2005	F	87	B19.0	I46.9	Diabetes, hypertension as AC
2005	F	3	B19.9	G93.6	Adult respiratory distress syndrome, Acute renal failure as IC

AC: additional cause of death
IC: intermediary cause of death
NS: None stated

Table 49: * ICD 10 codes in table 48

B15.0	Hepatitis A with hepatic coma
B15.9	Hepatitis A without hepatic coma
B19.0	Unspecified viral hepatitis with hepatic coma
B19.9	Unspecified viral hepatitis without hepatic coma
K72.9	Hepatic failure, unspecified
K74.6	Other and unspecified cirrhosis of liver
K76.9	Liver disease, unspecified
A41.9	Septicaemia, unspecified
I46.9	Cardiac arrest, unspecified
I50.9	Heart failure, unspecified
G93.6	Cerebral oedema
R57.0	Cardiogenic shock

The information in **table 48** can be used to compare with the "in-hospital-deaths" from the MKG-database, and the judgments from the experts in the previous section. Although the data are not linked we know that sex, year and age of these potential HAV deaths should, ideally, correspond for the regions of Flanders (and possibly partially Brussels). That is, if most people who die due to HAV, are admitted to hospital prior to dying. If the experts (partly) agreed on a specific death, we would expect it would be reflected on the death certificate of that person. Conversely, if the experts unanimously agreed that a specific death is definitely not due to hepatitis A, we would expect it not to be listed in **table 48**.

It is reassuring that all 26 MKG deaths (9 from Flanders), whom the experts unanimously considered unrelated to hepatitis A (see above), show no correspondence in terms of year, age and sex with the death certificate list in **table 48**. However, for only two of the potential in-hospital-deaths (listed in **table 47**) there seems to be a corresponding death certificate stating HAV as the underlying cause of death (**table 48**). According to the other information found on these 2 certificates, these deaths may indeed have been due to hepatitis. Additionally **table 48** lists 7 deaths which seem equally likely due to hepatitis A (they all were coded specifically with hepatitis A as the underlying cause of death, and do not bear other codes that contradict this ascertainment).

2.2.7 Liver transplantations attributable to hepatitis A

The European Liver Transplant Registry (ELTR) keeps track of liver transplantations carried out in Europe, with currently nearly all the European centers (137 centers in 23 countries) contributing information (see website www.eltr.org for a full list of contributing centres). Both the number of transplantation centers and the annual number of liver transplantations performed in Europe gradually increased since the ELTR was created (290 liver transplants in 1985, 3972 in 2000 and 5207 in 2004). [[108, 109]]

Since liver transplantations for hepatitis A are always urgent, the ELTR has a specific code A1: "acute hepatic failure. Fulminant or subfulminant hepatitis A" (personal communication, 2008, Mrs Francine Roggen, transplantation coordinator St Luc Hospital, Brussels)

Basic information on the liver transplantations reported to the ELTR, under the above code A1, were kindly provided to us for the period 1987-2007 by ELTR (personal communication, 2008, Dr Vincent Karam and Prof. dr. Rene Adam, ELTR). The information thus obtained is summarised in **table 50** and **Figure 21**.

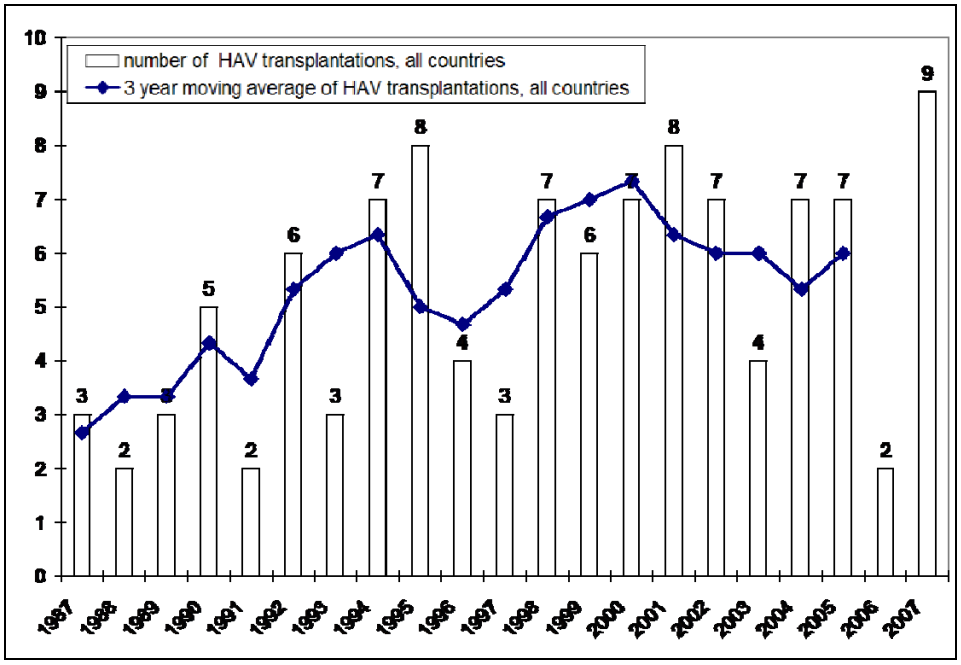
Clearly, caution is needed when interpreting these data, since the ratio of reporting versus existing liver transplantation centres varies between countries, as well as over time.

Nonetheless as shown in **table 50**, it is remarkable that Belgium has reported the largest absolute number of such transplantations of all reporting countries. Furthermore, if these numbers are related to population size, Belgium also reports the highest number of such liver transplantations relative to population size. This could be explained if Belgium was one of the first countries for which - from 1987 on- data were sent to ELTR from a large proportion of Belgian liver transplantation centres. Nonetheless, by taking only the time interval since the first ever reported liver transplantation per country into account, Belgium is only second to Switzerland (under the assumption that Switzerland reported only liver transplantations in the year 2007). Another explanation may therefore be that in Belgium a disproportionately large number of liver transplantations was performed on non-Belgians (which seems particularly likely at St Luc hospital), and Note that since 2003 there is a maximum cap of 5% on the proportion of liver transplantations that are allowed to be performed on non-Belgians in Belgium (personal communication Dr Hans Van Vlierberghe, Ugent, 2008).

Table 50: Number, age and relative frequency of liver transplantations for acute hepatic failure - fulminant or subfulminant hepatitis A, reported to the ELTR (1987-2007),

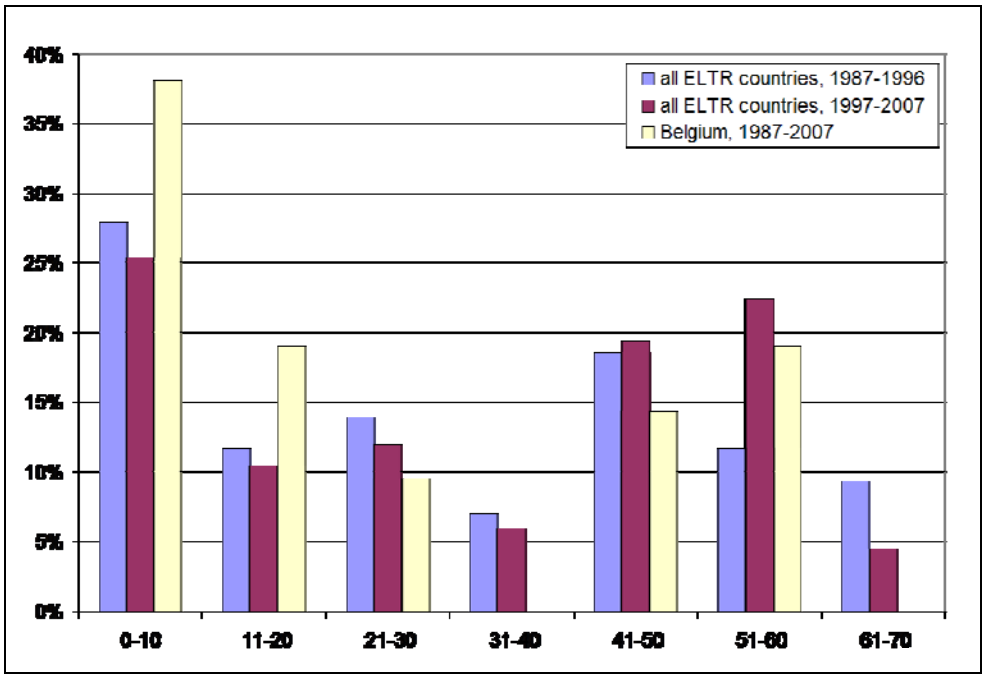
Country	Number	mean age	minimum age	maximum age	first year	last year	All years since first year of a reported HAV transplantation per country		Over the entire period 1987-2007	
							number per year	number per year per 10 million population	number per year	number per year per 10 million population
Belgium	21	24	3	59	1987	2007	1.00	0.94	1.00	0.94
Denmark	3	22	9	44	1990	1994	0.17	0.31	0.14	0.26
France	18	41	12	64	1987	2007	0.86	0.14	0.86	0.14
Germany	19	45	11	66	1989	2007	1.00	0.12	0.90	0.11
Ireland	1	26	26	26	2000	2000	0.13	0.29	0.05	0.11
Norway	2	46	38	54	2001	2004	0.29	0.61	0.10	0.20
Poland	6	24	7	54	2001	2007	0.86	0.22	0.29	0.07
Portugal	4	11	3	28	1999	2005	0.44	0.42	0.19	0.18
Spain	6	22	3	49	1990	2003	0.33	0.01	0.29	0.01
Sweden	1	48	48	48	1998	1998	0.10	0.11	0.05	0.05
Switzerland	1	42	42	42	2007	2007	1.00	1.33	0.05	0.06
The Netherlands	3	21	3	52	1998	2007	0.30	0.18	0.14	0.09
The UK	14	26	3	61	1990	2005	0.78	0.13	0.67	0.11
Turkey	5	7	3	10	2000	2007	0.63	0.09	0.24	0.03

Figure 21: Number of liver transplantations for acute hepatic failure - fulminant or subfulminant hepatitis A, reported to the ELTR (1987-2007), and 3 year moving average



The age distribution in **figure 22** , illustrates that, despite the higher proportion of asymptomatic and mild HAV infections in children versus adults, in Belgium, as well as the other reporting centres, a substantially larger proportion of hepatitis A liver transplants occurred in patients < 10 years of age, consistently over time since 1987.

Figure 22: Age distribution of transplant recipients for acute hepatic failure - fulminant or subfulminant hepatitis A in the ELTR database, 1997-2007 versus 1987-1996 for all ELTR European countries combined and Belgium, respectively



We attempted to verify the ELTR data for Belgium by contacting the 6 Belgian liver transplantation centres individually in order to enquire about the number of liver transplantations performed for liver failure caused by hepatitis A virus, covering at least the perod since the year 2000. At the University Hospitals of Antwerpen, Leuven and Erasmus (Brussels) none could be recalled. At the University Hospital of Liege none was recollected in the period 2000-2008, but one had been performed in 1992 on a 15 year old girl. Furthermore, since 2000 there had also been one such transplantation at the University Hospital of Gent, in a 64 year old patient in 2008, and two such transplantations at the University Hospital of St Luc (Brussels), in a 3 year old and in a 61 year old in the years 2001 and 2008, respectively. Table 51 shows the differences between the estimates by the individual liver transplant centres and the ELTR. Note that the collumns in table 51 do not only refer to different databases, but also to different periods, and that the table illustrates that the various sources give substantially different estimates (i.e. the last collumn is not meant to be the sum of the earlier collumns, though in theory there should be a better match than what we observe here in practice.

Table 51: Number of hepatitis A caused liver transplantations in the 6 Belgian transplantation centres, based on recollection or internal database, personal communications (2008) and data extractions from the ELTR database (1987-2007)

Hospital and person contacted (october 2008)	Number of transplants in the period 2000-2008	Recollected or recorded number of HAV caused liver transplantations ever[a]	Number of HAV caused liver transplantations as communicated by ELTR, 2000-2007	Number of HAV caused liver transplantations as communicated by ELTR, 1987-2007
University hospital Antwerpen (Prof dr Peter Michielsen)	0	0 (b)	0	0
University hospital Leuven (Mr Joachim Deroey)	0	0 (b)	1	2 (aged 48 in 2000 and aged 59, in 1995)
University hospital Liège (Mr Josée Monard)	0	1 (aged 15, in 1992) (c)	0	1 (aged 14, in 1992)
University hospital St Luc, Brussels (Mrs Francine Roggen)	2 (aged 61 in 2008 and aged 3 in 2001)	12 (d)	2 (aged 4 in 2007 and aged 13 in 2001)	13
University hospital Gent (Mr Luc Colenbie)	1 (aged 64 in 2008)	1 (e)	2	3 (aged 17 in 1999, aged 52 in 2006 and aged 57 in 2006)
University hospital Erasmus, Brussels (Mrs Elianne Angenon)	0	0 (b)	1	2 (aged 29 in 1987 and aged 55 in 2004)

(a) since these centres started performing liver transplantations at different points in time before the year 2000, and the information on hepatitis A as the underlying cause of the transplantations is not uniformly recorded or recollected in every centre, the information in this collumn should be considered less reliable than the information relating to the period 2000-2008.
(b) institutional recollection
(c) institutional recollection and database,
(d) checked database from the year 1984 onwards
(e) checked database from the year 2000 onwards only

From the Minimal Clinical Data (MCD)-database, it should theoretically be possible to also obtain information on liver transplantations. In order to select transplantations that are due to hepatic failure caused by HAV infection, we asked the four clinical experts , who judged the attributability of deaths in section 2.2.6.1 above, again for their opinion. Based on the associated codings, usually the transplantation seemed to have been indicated because of other pathologies, such as end-stage alcoholic liver disease, hepatocellular carcinoma or hepatitis B. However for 1 transplantation in a 13 year old patient (hospitalised in the year 2001), none of the experts excluded the possibility that hepatitis A was the underlying cause (highlighted in **table 52**). These results were anonimised on purpose, to prevent mutual influence between the experts.

Table 52: Age, sex, nationality and expert judgment of liver transplantations in Belgium (2000-2004), based on Minimal Clinical Data for patients with codes referring to both hepatitis A and liver transplantation

Sex	Age	Nationality	Death	Expert 1	Expert 2	Expert 3	Expert 4
M	57	2	0	NO	NO	NO	NO
M	40	2	0	MAYBE	NO	NO	NO
F	53	1	0	NO	NO	NO	NO
M	13	3	0	YES	MAYBE	MAYBE	MAYBE
M	67	1	0	NO	NO	NO	NO
M	55	1	0	MAYBE	MAYBE	NO	NO

* Nationality 0: unknown; 1: Belgian; 2: Non-Belgian but within the EU, 3: Non-Belgian outside the EU.
NO: Unlikely due to hepatitis A
MAYBE: possibly due to hepatitis A
YES: Likely due to hepatitis A

Comparing the suspected hepatitis A caused liver transplantations in **table 52** with those from the other sources in **table 51**, there seems to be cause for concern about the reliability of these different sources. Indeed, in the period 2000-2004, the ELTR database contains 4 HAV patients who underwent liver transplantations in one of the Belgian centres, one of whom has a matching age and year with the suspected record in the Minimal Clinical Database. Over the same period, the individually contacted centres recalled only 1 such patient, whose age did not match with any of the patients from the other two sources (one could speculate, however, about a potential typographical error between 3 and 13, since the 3 year old patient reported by St Luc hospital in 2001, matches the 13 year old patient in terms of sex, year and nationality in the MCD (and ELTR)).

Summarising the Belgian data for the period 2000-2008, we conclude there were at least 3 liver transplantations caused by hepatitis A (based on individual centres' reporting), and possibly 9 (based on all sources combined (i.e. column 2 shows 3 and column 4 shows 6 liver transplantations for the period 2000-2007/8, while assuming the 13y old patient recorded in the Minimal Clinical Data is the same 13 year old patient reported to ELTR this sums to 9), or between 0.33 and 1 per year, on average.

Over the period 1987-2007, there were at least 14, and possibly 21 such liver transplantations, or between 0.67 and 1 per year. Since other sources of infectious disease data we use in the current study to make simulations, relate to the epidemiological situation in the more recent period, we calibrate the models using this information on transplantation relating to the period 2000-2008.

In the simulation models we assume therefore that in Belgium the occurrence of HAV liver transplantations currently varies between 0.33 and 1 per year.

2.3 PARAMETER MEAN VALUES AND THEIR DISTRIBUTIONS FOR THE SIMULATIONS

Additional to the intrinsic model structure assumptions described in section 3.1 below, **tables 53** and **54** list the various parameters, their mean values and distributions (which were fitted, based as much as possible, on the data described in the above sections) used in the simulations undertaken to produce estimates of cost-effectiveness in this report.

Table 53: Parameter mean values, distributions and data sources for non age specific parameters

Non-age specific data	Mean (90% interval)	Distribution	Source
Miscellaneous			
Disc costs	0.03	NA	KCE-guidelines for Pharmacoeconomic evaluations
Disc effects	0.015	NA	KCE-guidelines for Pharmacoeconomic evaluations
Coverage vaccine	0.95	NA	National immunisation survey, Flanders-Wallonia, unpublished 2008
vaccine protective efficacy	0.95 (0.82-0.99)	Lognormal	Innis et al, 1994, JAMA
sensitivity	0.98 (0.980-0.995)	Uniform	Desbois, 2005, Gastroenterol Clin Biol
specificity	0.99 (0.994-0.999)	Uniform	Desbois, 2005, Gastroenterol Clin Biol
compliance test (min-max)	0.5-0.8	Uniform	Our assumption
Direct unit costs			
GP visit	21.53	NA	https://www.riziv.fgov.be/
GP home visit (additional cost)	10.79	NA	https://www.riziv.fgov.be/
specialist visit	29.73	NA	https://www.riziv.fgov.be/
Motillium	8.28	NA	http://www.bcfi.be
Maalox	8.45	NA	http://www.bcfi.be
Immodium Instant	7.21	NA	http://www.bcfi.be
Vitamine B	3.50	NA	http://www.bcfi.be
Ceterizine	4.14	NA	http://www.bcfi.be
Blood extraction	42.22	NA	Communication with medical lab
Echography	53.75	NA	https://www.riziv.fgov.be/

emergency care	18.30	NA	https://www.riziv.fgov.be/
vaccine	45.66	NA	http://www.bcfi.be
Administration cost of vaccine	21.53	NA	https://www.riziv.fgov.be/
Cost per test	22.41	NA	Communication with medical lab
Cost of a livertransplant	80,680	NA	Van Agthoven, 2001, Transplant international

Table 54: parameter mean values, 90% intervals, distributions and data sources for non age specific parameters

Age specific data (means, 90% intervals and distributions)	<15	15-30	>30	Distribution	Source
Deaths Scenario 1 (basecase)					
number of HAV deaths 1999-2005 Flanders	0.50 (0.05-0.95)	0.50 (0.05-0.95)	14.00 (9.5-18.5)	Uniform	Death certificates for Flanders 1999-2004 + 4 experts
probability to die from HAV 1999-2005	0.000000071 (0.3*10^-9 - 273.9*10^-9)	0.000000065 (0.3*10^-9 – 249.1*10^-9)	0.000000506 (0.306*10^-6 – 0.747*10^-6)	Beta	Death certificates for Flanders 1999-2004 + 4 experts
Deaths Scenario 2 (alternative)					
number of HAV deaths 2000-2004 Belgium	0.0003 (0.025*10^-3 - 0.776*10^-3)	0.33 (0.025-0.776)	6.33 (2.33-12.09)	Triangular	MKG data 2000-2004 + 4 experts
probability to die from HAV 2000-2004	0.000000000037 (0-0.594*10^-12)	0.000000034189 (0-151.1*10^-9)	0.000000188705 (84.4*10^-9 - 326.5*10^-9)	Beta	MKG data 2000-2004 + 4 experts
Liver transplantations					
number of LT 2000-2008 Belgium	2.33 (1.101-4.106)	1.00 (1-1)	1.67 (1.051-2.553)	Triangular	Belgian transplant centres + ELTR
probability LT from HAV 2000-2008	0.000000144 (30.6*10^-9 - 325.1*10^-9)	0.000000057 (2.9*10^-9 - 170.7*10^-9)	0.000000028 (3.8*10^-9 – 69.4*10^-9)	Beta	Belgian transplant centres + ELTR
Disease states					
Proportion of infections symptomatic	[0-0.89]	[0-0.89]	0.89	Beta	Prospective survey + Armstrong et al, 2002, Pediatrics
Proportion hospitalised/ symptomatic case	0.0319	0.0687	0.0475	Beta	MKG, subgroup selection (n=300)
Proportion jaundiced/ symptomatic case	0.85 (0.704-0.955)	0.95 (0.867-0.997)	0.95 (0.867-0.997)	Beta	prospective survey
Proportion coma/ hospitalised	0.01 (8.12*10^-3 –	0.01 (8.12*10^-3 –	0.01 (8.12*10^-3 –	Beta	MKG-data

	23.32*10^-3)	23.32*10^-3)	23.32*10^-3)		
Direct unit costs					
hospitalization	1252.35 (570-2444)	1539.90 (581- 2852)	1539.90 (581- 2852)	Loglogistic (<15); Weibull (≥15)	MKG-data
Indirect unit costs					
average cost per day of illness for employed persons	0.00	229.9 (>18) (205-255)	229.90 (205-255)	NA	Zebrazone report "Absenteïsme in België 2006"
werkgelegenheidsgraad (actieve bevolking/beroepsbevolking)	0.62	0.62	0.62	NA	National Bank of Belgium http://www.nbb.be/doc/DQ/N/DQ3/HISTO/INE0840.PDF
Quality of life					
Not hospitalized	0.6620 (0.028-1)	0.5633 (0.111-1)	0.5633 (0.111-1)	Discrete	EQ-5D, prospective survey
Hospitalized without coma	0.2892 (0.029-0.733))	0.2892 (0.029-0.733)	0.2892 (0.029-0.733)	Discrete	EQ-5D, prospective survey
Hospitalized with coma	-0.016300	-0.016300	-0.016300	NA	EQ-5D,PhD thesis I. Cleemput, KCE-guidelines for Pharmacoeconomic evaluations
Quality of life of a healthy life year, EQ-5D	1.00	1.00	1.00	NA	EQ-5D,PhD thesis I. Cleemput, KCE-guidelines for Pharmacoeconomic evaluations
Quality of life impact livertransplantation patients					
Hospital (days after LT)	0.36800	0.36800	0.36800	NA	Ratcliffe, 2005, Value in health
3 months after LT	0.57600	0.57600	0.57600	NA	Ratcliffe, 2005, Value in health
6 months after LT	0.60100	0.60100	0.60100	NA	Ratcliffe, 2005, Value in health
12 months after LT	0.62600	0.62600	0.62600	NA	Ratcliffe, 2005, Value in health
24 months after LT	0.62900	0.62900	0.62900	NA	Ratcliffe, 2005, Value in health
Medical resource use (units)					
GP visit (unhospitalized cases)	2.44 (0-5)	3.73 (1-7)	3.73 (1-7)	Poisson	Prospective survey
GP visit (hospitalized cases without coma)	2.44 (0-5)	3.73 (1-7)	3.73 (1-7)	Poisson	Prospective survey
GP visit (hospitalized cases with coma)	2.44 (0-5)	3.73 (1-7)	3.73 (1-7)	Poisson	Prospective survey
GP home visit (unhospitalized cases)	0.45 (0-2)	1.63 (0-4)	1.63 (0-4)	Poisson	Prospective survey

GP home visit (hosp. Cases without coma)	0.45 (0-2)	1.63 (0-4)	1.63 (0-4)	Poisson	Prospective survey
GP home visit (hosp. Cases with coma)	0.45 (0-2)	1.63 (0-4)	1.63 (0-4)	Poisson	Prospective survey
specialist visit (unhospitalized cases)	1.5 (0-4)	0.75 (0-2)	0.75 (0-2)	Poisson	Prospective survey
specialist visit (hospitalized cases without coma)	1.5 (0-4)	0.75 (0-2)	0.75 (0-2)	Poisson	Prospective survey
specialist visit (hospitalized cases with coma)	1.5 (0-4)	0.75 (0-2)	0.75 (0-2)	Poisson	Prospective survey
Motillium (unhospitalized cases)	0.16 (0.04-0.31)	0.07 (0.003-0.192)	0.07 (0.003-0.192)	Beta	Prospective survey
Motillium (hospitalized cases without coma)	0.16 (0.04-0.31)	0.07 (0.003-0.192)	0.07 (0.003-0.192)	Beta	Prospective survey
Motillium (hospitalized cases with coma)	0.16 (0.04-0.31)	0.07 (0.003-0.192)	0.07 (0.003-0.192)	Beta	Prospective survey
Maalox (unhospitalized cases)	0.00	0.13 (0.026-0.296)	0.13 (0.026-0.296)	Beta	Prospective survey
Maalox (hospitalized cases without coma)	0.00	0.13 (0.026-0.296)	0.13 (0.026-0.296)	Beta	Prospective survey
Maalox (hospitalized cases with coma)	0.00	0.13 (0.026-0.296)	0.13 (0.026-0.296)	Beta	Prospective survey
Immodium Instant (unhospitalized cases)	0.05 (0.002-0.153)	0.07 (0.003-0.192)	0.07 (0.003-0.192)	Beta	Prospective survey
Immodium Instant (hospitalized cases without coma)	0.05 (0.002-0.153)	0.07 (0.003-0.192)	0.07 (0.003-0.192)	Beta	Prospective survey
Immodium Instant (hospitalized cases with coma)	0.05 (0.002-0.153)	0.07 (0.003-0.192)	0.07 (0.003-0.192)	Beta	Prospective survey
Vitamine B (unhospitalized cases)	0.00	0.13 (0.026-0.296)	0.13 (0.026-0.296)	Beta	Prospective survey
Vitamine B (hospitalized cases without coma)	0.00	0.13 (0.026-0.296)	0.13 (0.026-0.296)	Beta	Prospective survey
Vitamine B (hospitalized cases with coma)	0.00	0.13 (0.026-0.296)	0.13 (0.026-0.296)	Beta	Prospective survey
Ceterizine (unhospitalized cases)	0.00	0.07 (0.003-0.192)	0.07 (0.003-0.192)	Beta	Prospective survey
Ceterizine (hospitalized cases without coma)	0.00	0.07 (0.003-0.192)	0.07 (0.003-0.192)	Beta	Prospective survey
Ceterizine (hospitalized cases with coma)	0.00	0.07 (0.003-0.192)	0.07 (0.003-0.192)	Beta	Prospective survey

Blood tests (unhospitalized cases)	2.15 (0-5)	2.93 (0-6)	2.93 (0-6)	Poisson	Prospective survey
Blood tests (hospitalized cases without coma)	2.15 (0-5)	2.93 (0-6)	2.93 (0-6)	Poisson	Prospective survey
Blood tests (hospitalized cases with coma)	2.15 (0-15)	2.93 (0-6)	2.93 (0-6)	Poisson	Prospective survey
Echography (unhospitalized cases)	0.1 (0-1)	0.46 (0-2)	0.46 (0-2)	Poisson	Prospective survey
Echography (hospitalized cases without coma)	0.1 (0-1)	0.46 (0-2)	0.46 (0-2)	Poisson	Prospective survey
Echography (hospitalized cases with coma)	0.1 (0-1)	0.46 (0-2)	0.46 (0-2)	Poisson	Prospective survey
emergency care (unhospitalized cases)	0.11 (0.02-0.237)	0.07 (0.003-0.192)	0.07 (0.003-0.192)	Poisson	Prospective survey
emergency care (hospitalized cases without coma)	0.11 (0.02-0.237)	0.07 (0.003-0.192)	0.07 (0.003-0.192)	Poisson	Prospective survey
emergency care (hospitalized cases with coma)	0.11 (0.02-0.237)	0.07 (0.003-0.192)	0.07 (0.003-0.192)	Poisson	Prospective survey
Prophylactic vaccination (unhospitalized cases)	2.55 (0-5)	3.8 (1-7)	3.8 (1-7)	Poisson	Prospective survey
Prophylactic vaccination (hospitalized cases without coma)	2.55 (0-5)	3.8 (1-7)	3.8 (1-7)	Poisson	Prospective survey
Prophylactic vaccination (hospitalized cases with coma)	2.55 (0-5)	3.8 (1-7)	3.8 (1-7)	Poisson	Prospective survey
days ill (unhospitalized cases)	17 (11-24)	18.75 (12-26)	18.75 (12-26)	Poisson	Prospective survey
days ill (hospitalized cases without coma)	23 (15-31)	23 (15-31)	23 (15-31)	Poisson	Prospective survey
days ill (hospitalized cases with coma)	23 (15-31)	23 (15-31)	23 (15-31)	Poisson	Prospective survey
lost days of work (unhospitalized cases)	5.45 (2-10)	28.25 (20-37)	28.25 (20-37)	Poisson	Prospective survey
lost days of work (hospitalized cases without coma)	5.45	42.7 (32-54)	42.7 (32-54)	Poisson	Prospective survey
lost days of work (hospitalized cases with coma)	5.45	42.7 (32-54)	42.7 (32-54)	Poisson	Prospective survey
Lost days of work after livertransplant	150	150	150	NA	Van Agthoven, 2001, Transplant international

Additionally, demographic data on the number of people in the general population and their life-expectancy by age were obtained from the Belgian National Institute of Statistics. For the deaths aged over 30 years (I.e. the majority of deaths), we assume that their life expectancy corresponds to the average life expectancy of the suspected HAV deaths from the death certificates, i.e. 5.72 years. Based on the age distribution of liver transplant recipients given above, it seems reasonable to assume that potential fatal hepatitis A cases between 30 and 60 years are usually avoided, since there are very few suspected HAV deaths reported in that age bracket.

Furthermore demographic data on people who were born as a Moroccan or Turkish national were derived from recent Belgian reports, and these data are summarised in **table 55**.

Table 55: Previous and current nationality and identification of children at risk of importing HAV infections in Belgium (sources: [110, 111])

	Currently non Belgian	Currently Belgian	Total	Estimated birth cohort
Moroccan at birth	81,287	165,037	246,324	2,803
Turkish at birth	40,403	94,274	134,677	1,533
DR Congo at birth	13,423	23,863	37,286	424
Moroccan or Turkish at birth	121,690	259,311	381,001	4,336
Moroccan or Turkish or Congolese at birth	135,113	283,174	418,287	4,760

The estimated birth cohort of children of Morocco and Turkey (and presumably of the DR Congo to a lesser extent) is assumed to represent the order of magnitude of a 1 year cohort of children who may return to their country of origin for a holiday period as a susceptible to hepatitis A, and return to Belgium carrying the infection and sparking a local outbreak (eg in school).

3 METHODS

3.1 GENERAL

The baseline costing perspective is that of the Belgian health care payer, which includes collective payments by the Belgian health care system, as well as co-payments for health care by patients. All cost data are expressed in Euro 2006. Our primary measure of relative efficiency is direct medical costs per Quality-Adjusted Life-Year (QALY), though a wider range of health outcomes is presented in incremental cost-effectiveness analyses. Time preference is accounted for by discounting costs at an annual constant rate of 3%, and effects at 1.5%. These analytical choices are in line with Belgian guidelines for economic evaluation in health care. More detailed discussion of each of the parameter estimates, and the theoretical foundation for these, given an analytical option to choose, is given in further subsections below. More basic discussions on methodological issues for the economic evaluation of vaccination programs were described previously.[112-114].

We consider the following options in our analyses, distinguishing two groups of analyses, using different models (see below):

1. analyses of universal strategies and targeted vaccination with an expected impact on the general epidemiology
    a. option 1: no vaccination
    b. option 2: vaccination of 2nd generation children of immigrants from high endemic areas
    c. option 3: vaccination of all Belgian infants
2. analyses for targeted strategies, aimed at groups without a substantial influence on population epidemiology of hepatitis A in Belgium (health care workers, patients with chronic liver disease)
    a. option 1: no vaccination
    b. option 2: vaccination of target group, irrespective of immunity status, at age of entry into the target group
    c. option3: vaccination of susceptibles in target group only (based on a test), at age of entry into the target group

Options of vaccinating contacts of cases, as is currently sporadically done in parts of Belgium in outbreak situations, is not explicitly considered as a separate option, mainly because it is unclear what the effectiveness of such actions would be through the use of vaccine. See for instance Sagliocca et al [73], with associated discussion correspondence. Furthermore such modelling would require yet another, differently structured mathematical model.

3.1.1 Mathematical model structures

3.1.1.1 General

In most infectious disease models, the population is made to flow between mutually exclusive compartments of susceptible (S), infectious (I) and recovered (R) (sometimes referred to as removed (immune) people). This basic structure (S-I-R) can be adapted, for instance, to include a latent phase with an Exposed (E) compartment (S-E-I-R), or an explicit phase of Maternal antibody protection (M) to make (M-S-E-I-R). When infection does not induce lifelong immunity, it would be important to revert to an S-I-S structure. For instance, an analysis of measles vaccination would minimally require a S-I-R structure (as after measles infection, one is immune for life), whereas pneumococcal conjugate vaccination would require an S-I-S structure (as one can be reinfected after infection with pneumococcus, and can therefore be considered to be susceptible again).

These compartments are the minimal set that govern the infectious disease processes, but for decision analysis, additional compartments are often useful, e.g. distinguishing compartments of people who are dead from the disease in question, or dead from other causes.

An important distinction must be made between 'static' and 'dynamic' models. In a dynamic transmission model, the force of infection (the probability that a susceptible person acquires infection per unit of time) can change over time. As more people are vaccinated, and the vaccine prevents transmission of the pathogen from infectious persons to susceptible persons, the proportion of infectious people in the population will decrease. Consequently, the force of infection acting on those remaining susceptible declines as well. A dynamic model takes this into account by cyclically recalculating the force of infection from the proportion of susceptible and infectious people at each point in time. In a static model the force of infection remains constant; i.e. although it can be defined as being age-dependent, in a static model the force of infection is assumed to be independent of the proportion of infectious people in the (age-specific) population at various time points. Typically, in dynamic models the transitions between health states are estimated by solving sets of differential equations in continuous age and/or time (i.e. at every moment). Alternatively, for practical reasons, discrete age and/or time (i.e. when events are assumed to occur over discrete time and/or age intervals (e.g. one year), instead of on a continuous basis) are often applied, especially to model the ageing process in dynamic models. In static models, time and age is typically equalized (by modelling a single ageing cohort), and is defined over discrete intervals, e.g. the observed incidence over one year is used to estimate the number of cases as the cohort ages by one year, in one discrete step (or "cycle" in a Markov model).[113] The pivotal choice in infectious disease modelling that aims to estimate the cost-effectiveness of vaccination is the choice between a static or a dynamic model.[113] Although other choices can be made about how the model is set up, such as deterministic or stochastic, grouped or individual based, open or closed, or how the simulation is performed, such as by solving sets of difference equations, or sets of differential equations, these are usually secondary to the static/dynamic choice in the framework of economic analysis of a vaccination programme. These "secondary" choices will also be more important for some situations than for others. [113] Static models are a priori suited for evaluation of the impact of vaccination if herd immunity does not play an important role – i.e. when the additional effectiveness per additional vaccinee is constant.[113] One particular example is an intervention targeted at a specific risk group that is not or does not contain an epidemiologically influential group for transmitting the pathogen. Immunizing such groups will not cause nonlinear differences in transmission to the groups in question or in the population as a whole, provided that the number of vaccinees remains relatively small compared with the total population size. Examples of the sort of vaccination programmes that fall into this category are hepatitis A virus (HAV) vaccination of health care workers, influenza and pneumococcal vaccination programmes targeted at the elderly or varicella-zoster virus vaccination of (susceptible) pre-adolescents or healthcare workers. Another example is where vaccination against an infection will not induce herd immunity, simply because the transmission of the infectious agent does not depend on the presence of infectious humans, e.g. tetanus and rabies.[113]

3.1.1.2 Hepatitis A model review

Universal strategies

In order to assess the effectiveness and cost-effectiveness of universal immunization versus current practice, modeling of HAV transmission dynamics is required. Static Markov models of HAV vaccination impact describing the evolution of epidemiological variables (susceptible, exposed or latent, infectious, recovered and vaccinated) in a single ageing cohort have been developed, mainly for the purpose of economic evaluation [83, 96], thus making abstraction from herd immunity effects.

Although this can be justified in some circumstances, if expected herd immunity impacts are such that choosing a static model to assess universal vaccination options could mislead decisions, a more sophisticated form of modeling is required.[112] Initially Markov models have been modified to account for this effect as much as possible. Velenzuela et al imputed observed within-cohort herd immunty effects to a single closed cohort [115]. In that way the herd immunity effects were underestimated because disease spread from personal contacts of cohort members to other susceptible persons was ignored.

Further improvement along that line came by considering within-cohort and out-of-cohort herd immunity effects for successive cohorts by Armstrong et al[116], and Rein et al[117]. In this way, the positive effects of herd immunity can be accounted for, but the negative effects cannot (eg, the shift in average age at infection under a decreasing force of infection).[113] However, such effects can only be adequately described in a dynamic age-structured model, in which the underlying infectious disease transmission process is modeled. The first model of this class notably explored the influence of age at vaccination [118]. It did not incorporate deaths (as it used a "square-shaped" survival curve). Another model investigated the switch from a high to a lower hepatitis endemic level [119]. Finally the latest type of model takes into account age-specific death rates as well as the historical decline of HA incidence in a low endemic country, namely Canada [120, 121]. In addition it considered the importation of infections by susceptible individuals traveling from Canada to high endemic countries. For that last model, the ordinary differential equations that govern the time evolution of state variables during each year are:[120]

$$\frac{dS_i}{dt} = -S_i \sum_{j=1}^{n} \beta_{ij} \frac{I_j}{N_j} - \tau_i S_i - g_i + fV_i$$

$$\frac{dE_i}{dt} = S_i \sum_{j=1}^{n} \beta_{ij} \frac{I_j}{N_j} + \tau_i S_i - \delta E_i$$

$$\frac{dI_i}{dt} = -\gamma_i I_i + \delta E_i$$

$$\frac{dR_i}{dt} = \gamma_i I_i$$

$$\frac{dV_i}{dt} = g_i - fV_i$$

where i is the age in years, n the number of age classes, S_i (respectively E_i, I_i, R_i, V_i) is the number of susceptible (respectively exposed, infectious, recovered, vaccinated) individuals of age i, N_j is the total number of individuals of age j, f is the mean rate at which vaccine-derived immunity wanes, $1/\delta$ is the mean latent period, $1/\gamma_i$ is the mean duration of infectiousness, β_{ij} is the rate at which a susceptible of age i becomes infected by contact with infectious individuals in age class j, τ_i is the rate at which a susceptible of age a becomes infected from travel in an endemic country, and g_i is the rate at which individuals of age i are vaccinated.

Death and ageing processes were included by applying the condition $X_{i+1} = (1-d_i)X_i$

at the start of each year for $1<i<n$, for the different epidemiological state variables (X represents S,E,I,R,V), where d_i is the per capita death rate in age i.

Birth was included by applying the condition

$$S_1 = b, \quad E_1 = 0, \quad I_1 = 0, \quad R_1 = 0, \quad V_1 = 0$$

at the start of each year, where b is the annual number of births. Birth and death rules were chosen in such a way that total population size and the size of each age class remained constant. Incidence data of reported data, an estimated rate of underreporting and seroprevalence data were combined using catalytic modeling to attempt to assess the true force of infection (15). Catalytic modelling uses integral equations to reconcile case reporting data (which are available for each year but are significantly under-reported) and seroprevalence data (which are a reliable indicator of past infection but do not indicate in which year the infection occurred). The reported number of cases by year and age class is adjusted for (a) the probability of jaundice and (b) under-reporting rates until the discrepancy with the expected seroprevalence in that year and age class is minimized.

Calculated transmission rates β_{ij} were largest in youngest age classes, and generally decreased along the diagonal of the matrix as one moves in the direction of older age classes, except for a noticeable increase around 30; the transmission rates also decreased in the direction of the cross-diagonal.

Targeted options in isolation

Until now, most targeted options have been analysed for the purpose of economic evaluation using a "classic" static Markov cohort model, as is the case for the large majority of any type of health technology assessment. We will not discuss these well known models here any further, other than referring to the review of economic evaluations below, and the associated appendices for a full list of published studies that have used these models.

For an analysis in Amsterdam, Postma et al[122] used a Poisson model to generate the number and size of outbreaks of hepatitis A arising from children of immigrant families In Amsterdam. In the current study, in view of the unpredictability of outbreaks in food handlers, we would have used a similar model structure to estimate the effectiveness of vaccination targeted at food handlers, if it had been possible to obtain reliable estimates on the number of foodhandlers in Belgium, and their rotation in and out their jobs. This, however, has not proved possible, and thus we will not investigate the possibility of targeted vaccination of food handlers in this report.

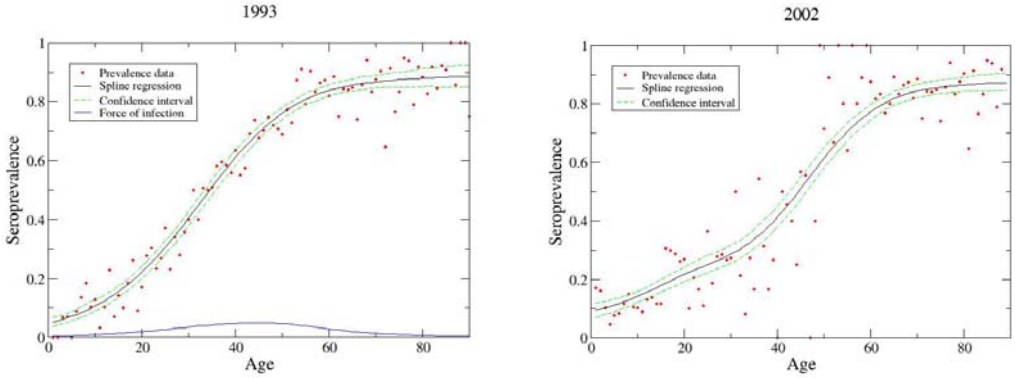
3.1.2 Model development

In this section we describe the models developed as part of the current project. The aims of these models are threefold. First, they help to understand qualitatively the changing HAV epidemiology in Belgium. Second, where appropriate, they are used to make quantitative projections of the disease burden in Belgium, given various scenarios of intervention. Third, both qualitative and quantitative models are used to motivate and identify effective and cost-effective options for HAV vaccination in Belgium.

3.1.2.1 Strategies with a general population impact

As already outlined in previous section 2.3.1.1, the transmission dynamics of Hepatitis A are not stationary in the sense that the force of infection is varying over time not only because the fraction of infected people changes but also because transmission decreases as a result of improved health and sanitary conditions. Consideration of summation data (eg, seroprevalence data) from a single period of time only can therefore be misleading.

Figure 23: Age-specific prevalence profiles for Belgium at nine years of interval. The data (red disks) are smoothed by a monotonic spline regression (black line) associated to 95 % confidence intervals (dashed green line).



As a matter of fact, in Belgium, the force of infection (blue line at the bottom) calculated from the prevalence curve in 1993 (**figure 23**, left panel) presents a maximum of 5% around age 45. This estimate is based on a single cross sectional sample, and is based on the assumption that, in the absence of vaccination, the force of HAV infection is constant through time.

Since we know this assumption is violated, we decided to estimate the force of infection instead from the changes in the seroprevalence profile between 1993 and 2002.

In what follows we show that these changes can be explained in a first approximation by changes in vaccination uptake rates, and demography, without the need to include a positive, non-zero force of infection.

We consider three epidemiologic states: susceptible (S), infectious (I) and recovered (R), thus including the latent state within the infectious state. Additionally, the period of maternal immunity is not explicitly modeled, and the implicit assumption here is that children under 6 months of age do not take part in the transmission process. Naturally acquired and vaccine-induced immunity are both assumed to be life-long. The virus is imported from endemic countries by travelers (or food) and is transmitted among the population via contacts between persons. The corresponding dimensionless unstructured SIR model for a growing population is

$$\frac{dS}{dt} = (1+\delta)(I+R) - \beta IS - (\tau+\nu)S$$
$$\frac{dI}{dt} = \beta IS - (1+\delta+\gamma)I + \tau S$$
$$\frac{dR}{dt} = \gamma I - (1+\delta)R + \nu S$$
$$S + I + R = 1$$

where S (respectively I, R) is the fraction of susceptible (respectively infectious, recovered) individuals.

The time scale unit is the average life time, L, of individuals in the population, δ is the growth rate of the population, β is the rate at which a susceptible becomes infected by contact with infectious individuals, τ is the rate at which a susceptible becomes infected from travel in an endemic country, ν is the rate at which individuals are vaccinated, $1/\gamma$ is the mean duration of infectiousness.

Let's assume that there are no infected individuals, $I = 0$. This implies that there is no effective importation of the virus, $\tau = 0$. The equations for S and R become linear and can be easily integrated.

The demographic data used in the following calculations were taken from EUROSTAT. The average life time in Belgium estimated from the Belgian life tables is $L = 75$. The population growth rate between 1993 and 2002, and the vaccination rate calculated from the annual sales figures (see section 2.1.2) are

$$\delta = \frac{1}{9}\ln\left(\frac{N^{(2002)}}{N^{(1993)}}\right)L \approx 2.6\times10^{-3}L \quad \nu \approx 4.5\times10^{-3}L$$

where $N^{(x)}$ is the total population for year x. The initial conditions for the fractions of susceptible and recovered individuals are determined by the weighted average of the prevalence π in 1993

$$1 - \left\langle \pi^{(1993)} \right\rangle \approx 49\% \quad \Rightarrow \quad S(0) = 0.49$$
$$\left\langle \pi^{(1993)} \right\rangle \approx 51\% \quad \Rightarrow \quad R(0) = 0.51$$

The weighted average is calculated by multiplying the prevalence in each age-class by the number of individuals in that age-class and dividing the sum of these results by the total number of individuals in the population. The increase of the fraction of susceptible and the decrease of the fraction of recovered individuals predicted by the analytical solutions after 9 years perfectly match with the weighted average of the prevalence π in 2002

$$S\left(\frac{9}{L}\right) \approx 0.54 \quad 1-\left\langle \pi^{(2002)} \right\rangle \approx 54\%$$
$$R\left(\frac{9}{L}\right) \approx 0.46 \qquad \left\langle \pi^{(2002)} \right\rangle \approx 46\%$$

Hence there is no general endemic level of HAV in Belgium (since we started by assuming that the number of infected individuals is negligible).

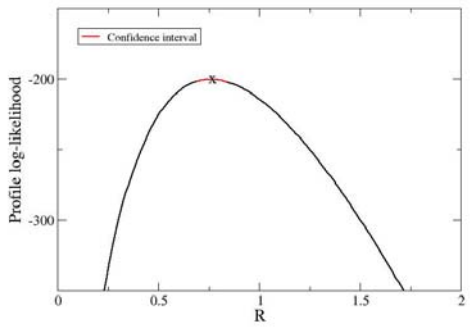
Note that endemicity relates to the propensity to spread locally, and not to the occurrence of infection and disease.

This conclusion is further supported by the statistical analysis of the Belgian outbreak data, reported in section 2.2.2. The Borel-Tanner distribution

$$P(s=n) = \frac{R^{n-1}e^{-Rn}n^{n-2}}{(n-1)!} \qquad n = 1,2,3,...$$

expresses the probability to observe an outbreak of size *n* as a function of the effective reproduction number *R* under the assumption of random mixing.[123] The number of infectious contacts made by an infected individual is assumed to be Poisson distributed with mean *R*. The results of the analysis are summarized in **figure 24**. Food-born outbreaks, that are characterized by large sizes, have been excluded because they represent contamination from a common source rather than transmission among people. The maximum log-likelihood is obtained for *R* = 0.76 with a 95% confidence interval (0.69,0.84). With *R* < 1, the infection cannot not be endogenously sustained by transmission.

Figure 24: Profile log-likelihood of the effective reproduction number with estimated value (x-mark) and 95% confidence interval (red line) based on the Borel-Tanner distribution.



However, since in these outbreak investigations - despite the often substantial efforts of the health inspection to trace all cases - not all infections are recorded, we may have systematically underestimated the effective reproduction number based on these outbreak data. On the other hand, it is also true that smaller clusters of infections are more often missed (completely) than larger clusters, and that these data comprise data from the province of Antwerp where only cluster information of at least 5 cases was available, whereas the median cluster size in other provinces is 2 or 3. Clearly, the latter limitation of the data inevitably led to an opposing overestimation of the effective reproduction number. Nonetheless, we concentrated on the possibility that we underestimated the effective reproduction number by conducting sensitivity analyses by increasing the cluster size of these outbreaks by multiplication factors to account for underreporting, distinguishing outbreak situations with mainly children involved, in schools and day care centres (and a high proportion of asymptomatic cases) from those with mainly adults involved in households (and a low proportion of asymptomatic cases).

As the below **table 56** indicates, the estimated effective reproduction number subjected to this form of uncertainty continues to show that HAV is very likely non-endemic in Belgium.

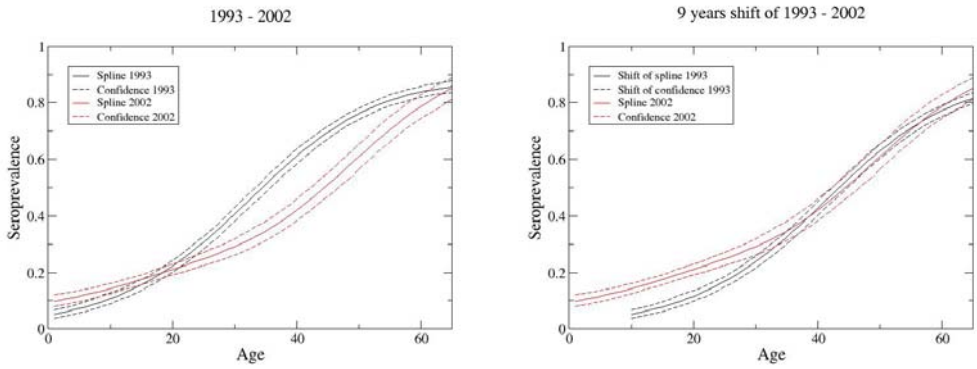
Table 56: Estimated effective reproduction number with 95% confidence interval in brackets, based on the Borel-Tanner distribution after multiplication of cluster sizes in family outbreaks (i.e. mainly adults) by the factors in the first column, and the cluster sizes in the school/day care centre outbreaks by the factors in the first row.

Family /School	1	2	4	8
1	0.76 (0.69-0.84)	0.83 (0.75-0.93)	0.90 (0.83-0.98)	0.94 (0.89-1.00)
2	0.85 (0.76-0.94)	0.88 (0.80-0.96)	0.92 (0.85-0.99)	0.95 (0.90-1.00)
4	0.91 (0.84-0.98)	0.92 (0.86-0.99)	0.94 (0.88-1.00)	0.96 (0.91-1.01)
8	0.95 (0.90-1.01)	0.96 (0.91-1.01)	0.96 (0.92-1.01)	0.97 (0.93-1.01)

Hence, there is convincing evidence that HAV is very unlikely to be endemic in Belgium, implying that the pool of infected individuals in Belgium is continuously replenished by importation of the virus by travelers, who acquired infection while abroad (and arguably imported food items, although no evidence currently points in this direction).

It appears clearly in **Figure 25** that, in contrast with old people, the prevalence is increasing between 1993 and 2002 for young people below 20 years of age. On the other hand cohorts aged over 30 years in 1993 experienced almost no infection for the period leading up to 2002.

Figure 25: Comparison of age-specific prevalence profiles (full lines associated to 95 % confidence intervals in dashed lines) for Belgium in time only and following cohorts.



We consider the simplest age-structured SIR model able to take account of this behavior. The population is divided according to age into three groups: youngsters up to age a_1, young adults up to age a_2 and older adults. For simplicity but at the expense of some quantitative inaccuracy, we impose that the population size in each age-class remains constant over time. The time scale unit is chosen to be the average life time, L, in the medium age-class.

The set of dimensionless ordinary differential equations governing the evolution of the different epidemiological fractions of the population in each age-class is:

$$\frac{dS_0}{dt} = (\alpha+\mu)[-\varepsilon\eta S_0 + (1-\varepsilon\eta)(I_0+R_0)] - S_0\sum_{j=0}^{2}\beta_{0j}I_j - (\tau_0+\varepsilon\nu_0)S_0$$

$$\frac{dS_1}{dt} = \alpha\rho_0(S_0-S_1) - S_1\sum_{j=0}^{2}\beta_{1j}I_j - (\tau_1+\varepsilon\nu_1)S_1$$

$$\frac{dS_2}{dt} = \rho_1(S_1-S_2) - S_2\sum_{j=0}^{2}\beta_{2j}I_j - (\tau_2+\varepsilon\nu_2)S_2$$

$$\frac{dI_0}{dt} = -(\alpha+\mu)I_0 + S_0\sum_{j=0}^{2}\beta_{0j}I_j - \gamma_0 I_0 + \tau_0 S_0$$

$$\frac{dI_1}{dt} = \alpha\rho_0(I_0-I_1) + S_1\sum_{j=0}^{2}\beta_{1j}I_j - \gamma_1 I_1 + \tau_1 S_1$$

$$\frac{dI_2}{dt} = \rho_1(I_1-I_2) + S_2\sum_{j=0}^{2}\beta_{2j}I_j - \gamma_2 I_2 + \tau_2 S_2$$

$$\frac{dR_0}{dt} = (\alpha+\mu)[\varepsilon\eta(S_0+I_0) - (1-\varepsilon\eta)R_0] + \gamma_0 I_0 + \varepsilon\nu_0 S_0$$

$$\frac{dR_1}{dt} = \alpha\rho_0(R_0-R_1) + \gamma_1 I_1 + \varepsilon\nu_1 S_1$$

$$\frac{dR_2}{dt} = \rho_1(R_1-R_2) + \gamma_2 I_2 + \varepsilon\nu_2 S_2$$

$$1 = S_0(t) + I_0(t) + R_0(t)$$

$$1 = S_1(t) + I_1(t) + R_1(t)$$

$$1 = S_2(t) + I_2(t) + R_2(t)$$

where S_i (respectively I_i, R_i) is the fraction of susceptible (respectively infectious, recovered) individuals in age-class i, $1/\alpha$ is the size of the first age-class, ρ_i are the population size ratios of the three age-classes, μ is the mean mortality in the first age-class, η is the proportion of vaccinated newborns, ε is the vaccine efficacy, τ_i is the rate at which a susceptible in age-class i becomes infected from travel in an endemic country, ν_i is the rate at which individuals in age-class i are vaccinated, $1/\gamma_i$ is the mean duration of infectiousness in age-class i, β_{ij} is the rate at which a susceptible in age-class i becomes infected by contact with infectious individuals in age-class j.

There is no systematic vaccination of newborns until now, $\eta = 0$. We include youngsters in the first age-class up to their sixteenth birthday, a_1 = 15 y, because it corresponds to the upper age limit of the pediatric formulation for children, for which we estimated vaccine uptake separately (see section 2.1.2). We include young adults in the second age-class up to their thirty first birthday, a_2 = 30 y. We assume a total average lifetime of 75 years with negligible mortality in the first age-class. Setting L = 15, we have

$$\alpha = \frac{L}{15} = 1 \qquad \text{and} \qquad \mu = 0$$

The average vaccination rates by age-class between 1993 and 2002 calculated from Belgian annual sales figures are

$$\nu_0 = 0.26\times10^{-2}L$$

and

$$\nu_1 = 0.76\times10^{-2}L \quad \nu_2 = 0.4\times10^{-2}L \quad a_v \le 55\,\text{y}$$

or

$$\nu_1 = 1.01\times10^{-2}\,L \quad \nu_2 = 0.32\times10^{-2}\,L \quad a_\nu \le 45\,\text{y}$$

according to whether the maximum age of vaccination is assumed to be 55 or 45 years. The average clearance rate of the infection by age-class is

$$\gamma_0 = \frac{52}{3}L, \qquad \gamma_1 = \frac{52}{2.5}L \qquad \text{and} \qquad \gamma_2 = \frac{52}{2.5}L$$

The population size ratios of the three age-classes for Belgium are

$$\rho_0 = \frac{N_0}{N_1} = \frac{9}{10} \qquad \text{and} \qquad \rho_1 = \frac{N_1}{N_2} = \frac{1}{3}$$

where N_i is the total number of individuals in age-class *i*. To estimate the maximum import rates τ_i, we assume no endogenous transmission

$$\beta_{ij} = 0$$

The ordinary differential equations become linear and can be solved analytically.

The initial conditions for the fractions of susceptible and recovered individuals in each age-class are determined by the corresponding weighted prevalence in 1993

$$\left\langle \pi_0^{(1993)} \right\rangle = 10\% \quad (8\% - 11\%)$$
$$\left\langle \pi_1^{(1993)} \right\rangle = 28\% \quad (26\% - 30\%)$$
$$\left\langle \pi_2^{(1993)} \right\rangle = 73\% \quad (70\% - 75\%)$$

$$\begin{array}{rlll} & S_0(0) = 0.9 \quad (0.89-0.92) & R_0(0) = 0.1 \quad (0.08-0.11) - I_0(0) \\ \Rightarrow & S_1(0) = 0.72 \quad (0.7-0.74) & R_1(0) = 0.28 \quad (0.26-0.3) - I_1(0) \\ & S_2(0) = 0.27 \quad (0.25-0.3) & R_2(0) = 0.73 \quad (0.7-0.75) - I_2(0) \end{array}$$

where 95% confidence intervals are indicated between brackets. The final conditions are calculated similarly from data in 2002

$$\left\langle \pi_0^{(2002)} \right\rangle = 13\% \quad (12\% - 15\%)$$
$$\left\langle \pi_1^{(2002)} \right\rangle = 24\% \quad (21\% - 26\%)$$
$$\left\langle \pi_2^{(2002)} \right\rangle = 62\% \quad (58\% - 66\%)$$

$$\begin{array}{rlll} & S_0\left(\frac{9}{L}\right) = 0.87 \quad (0.85-0.88) & R_0\left(\frac{9}{L}\right) = 0.13 \quad (0.12-0.15) - I_0\left(\frac{9}{L}\right) \\ \Rightarrow & S_1\left(\frac{9}{L}\right) = 0.76 \quad (0.74-0.79) & R_1\left(\frac{9}{L}\right) = 0.24 \quad (0.21-0.26) - I_1\left(\frac{9}{L}\right) \\ & S_2\left(\frac{9}{L}\right) = 0.38 \quad (0.34-0.42) & R_2\left(\frac{9}{L}\right) = 0.62 \quad (0.58-0.66) - I_2\left(\frac{9}{L}\right) \end{array}$$

The maximum import rates τ_i are estimated from the exact solutions for the fractions of susceptible individuals S_i. For the first age-class we have

$$\frac{\tau_0}{L} = 1\%\text{y}^{-1} \qquad 0.74\%\text{y}^{-1} \le \frac{\tau_0}{L} \le 1.53\%\text{y}^{-1} \qquad \varepsilon = 100\%$$
$$\frac{\tau_0}{L} = 1.01\%\text{y}^{-1} \quad 0.75\%\text{y}^{-1} \le \frac{\tau_0}{L} \le 1.54\%\text{y}^{-1} \qquad \varepsilon = 95\%$$
$$\frac{\tau_0}{L} = 1.05\%\text{y}^{-1} \quad 0.79\%\text{y}^{-1} \le \frac{\tau_0}{L} \le 1.58\%\text{y}^{-1} \qquad \varepsilon = 80\%$$

The lower and upper bounds for τ_0 correspond respectively to the smallest and largest decrease in S_0 between 1993 and 2002 according to the 95% confidence intervals. The value of the import rate τ_0 is of course a decreasing function of the vaccine efficacy ε. For the second age-class we have

$$\frac{\tau_1}{L} = -0.23\%\text{y}^{-1} \quad -1.01\%\text{y}^{-1} \le \frac{\tau_1}{L} \le 0.35\%\text{y}^{-1} \quad \varepsilon = 100\%$$
$$\frac{\tau_1}{L} = -0.19\%\text{y}^{-1} \quad -0.97\%\text{y}^{-1} \le \frac{\tau_1}{L} \le 0.39\%\text{y}^{-1} \quad \varepsilon = 95\% \quad a_v \le 55\,\text{y}$$
$$\frac{\tau_1}{L} = -0.08\%\text{y}^{-1} \quad -0.86\%\text{y}^{-1} \le \frac{\tau_1}{L} \le 0.5\%\text{y}^{-1} \quad \varepsilon = 80\%$$

or

$$\frac{\tau_1}{L} = -0.48\%\text{y}^{-1} \quad -1.26\%\text{y}^{-1} \le \frac{\tau_1}{L} \le 0.1\%\text{y}^{-1} \quad \varepsilon = 100\%$$
$$\frac{\tau_1}{L} = -0.43\%\text{y}^{-1} \quad -1.21\%\text{y}^{-1} \le \frac{\tau_1}{L} \le 0.15\%\text{y}^{-1} \quad \varepsilon = 95\% \quad a_v \le 45\,\text{y}$$
$$\frac{\tau_1}{L} = -0.28\%\text{y}^{-1} \quad -1.06\%\text{y}^{-1} \le \frac{\tau_1}{L} \le 0.3\%\text{y}^{-1} \quad \varepsilon = 80\%$$

depending on the assumed maximum age of vaccination. The lower and upper bounds for τ_1 correspond respectively to the largest and smallest increase in S_1. The value of τ_1 decreases with ε as expected. It increases with the maximum age of vaccination. For the last age-class we have

$$\frac{\tau_2}{L} = -1.3\%\text{y}^{-1} \quad -3.29\%\text{y}^{-1} \le \frac{\tau_2}{L} \le 1.14\%\text{y}^{-1} \quad \varepsilon = 100\%$$
$$\frac{\tau_2}{L} = -1.28\%\text{y}^{-1} \quad -3.28\%\text{y}^{-1} \le \frac{\tau_2}{L} \le 1.16\%\text{y}^{-1} \quad \varepsilon = 95\% \quad a_v \le 55\,\text{y}$$
$$\frac{\tau_2}{L} = -1.22\%\text{y}^{-1} \quad -3.21\%\text{y}^{-1} \le \frac{\tau_2}{L} \le 1.22\%\text{y}^{-1} \quad \varepsilon = 80\%$$

or

$$\frac{\tau_2}{L} = -1.22.\%\text{y}^{-1} \quad -3.22\%\text{y}^{-1} \le \frac{\tau_2}{L} \le 1.22\%\text{y}^{-1} \quad \varepsilon = 100\%$$
$$\frac{\tau_2}{L} = -1.21\%\text{y}^{-1} \quad -3.2\%\text{y}^{-1} \le \frac{\tau_2}{L} \le 1.23\%\text{y}^{-1} \quad \varepsilon = 95\% \quad a_v \le 45\,\text{y}$$
$$\frac{\tau_2}{L} = -1.16\%\text{y}^{-1} \quad -3.15\%\text{y}^{-1} \le \frac{\tau_2}{L} \le 1.28\%\text{y}^{-1} \quad \varepsilon = 80\%$$

depending on the assumed maximum age of vaccination. The lower and upper bounds for τ_2 correspond to the largest and smallest increase in S_2 respectively. The value of τ_2 decreases with ε as should be. In contrast with the previous age-class, it decreases with the maximum age of vaccination. In all cases, the maximum import rate first decreases and then increases, but to a lesser extent, with age. Negative values are unphysical and are replaced by zero in the following.

We now take the situation in 2002 as initial condition

$$\left\langle \pi_0^{(2002)} \right\rangle = 13\% \quad (12\% - 15\%)$$
$$\left\langle \pi_1^{(2002)} \right\rangle = 24\% \quad (21\% - 26\%)$$
$$\left\langle \pi_2^{(2002)} \right\rangle = 62\% \quad (58\% - 66\%)$$

$$\begin{array}{ll} & 0.85 \le S_0(0) \le 0.88 \quad 0.12 \le R_0(0) + I_0(0) \le 0.15 \\ \Rightarrow & 0.74 \le S_1(0) \le 0.79 \quad 0.21 \le R_1(0) + I_1(0) \le 0.26 \\ & 0.34 \le S_2(0) \le 0.42 \quad 0.58 \le R_2(0) + I_2(0) \le 0.66 \end{array}$$

To emphasize the existence of a steady state for the fraction of infectious individuals, that results from the balance between import and clearance of infections, we start with no infection: $I_0(0)=0$, $I_1(0)=0$ and $I_2(0)=0$. After 6 years of evolution, the prediction of the situation in 2008 is

$$0.83 \le S_0\left(\frac{6}{L}\right) \le 0.88 \quad 0.12 \le R_0\left(\frac{6}{L}\right) \le 0.17$$
$$0.73 \le S_1\left(\frac{6}{L}\right) \le 0.79 \quad 0.21 \le R_1\left(\frac{6}{L}\right) \le 0.27$$
$$0.36 \le S_2\left(\frac{6}{L}\right) \le 0.46 \quad 0.54 \le R_2\left(\frac{6}{L}\right) \le 0.64$$

$$3.8\times10^{-4} \le I_0\left(\frac{6}{L}\right) \le 7.5\times10^{-4}$$

$$1.1\times10^{-6} \le I_1\left(\frac{6}{L}\right) \le \begin{matrix} 1.4\times10^{-4} & \varepsilon = 95\% \\ 1.8\times10^{-4} & \varepsilon = 80\% \end{matrix} \quad a_v \le 55\text{y}$$

$$1.1\times10^{-6} \le I_1\left(\frac{6}{L}\right) \le \begin{matrix} 0.5\times10^{-4} & \varepsilon = 95\% \\ 1.1\times10^{-4} & \varepsilon = 80\% \end{matrix} \quad a_v \le 45\text{y}$$

$$1.2\times10^{-9} \le I_2\left(\frac{6}{L}\right) \le 2.2\times10^{-4}$$

Comparing the situation in 2002 with the prediction in 2008, the trend is a decrease in the fraction of susceptible individuals (increase in the fraction of recovered ones) in the first two age-classes (children and young adults) and a more pronounced increase in the fraction of susceptible individuals (decrease in the fraction of recovered ones) in the third age-class (older adults). The predicted numbers of infected (or infectious) individuals are

$$N_0 \approx 1.8\times10^6 \quad \Rightarrow \quad 680 \le I_0^{(2008)} \le 1360$$

$$N_1 \approx 2\times10^6 \quad \Rightarrow \quad 0 \le I_1^{(2008)} \le \begin{matrix} 280 & \varepsilon = 95\% \\ 360 & \varepsilon = 80\% \end{matrix} \quad a_v \le 55\text{y}$$

$$N_1 \approx 2\times10^6 \quad \Rightarrow \quad 0 \le I_1^{(2008)} \le \begin{matrix} 100 & \varepsilon = 95\% \\ 220 & \varepsilon = 80\% \end{matrix} \quad a_v \le 45\text{y}$$

$$N_2 \approx 6.6\times10^6 \quad \Rightarrow \quad 0 \le I_2^{(2008)} \le 1450$$

In the following, we take the vaccine efficacy to be equal to its mean, ε=95%, and we assume that the maximum age of vaccination is fifty five years old, $a_v \le 55$y.

In order to estimate the nonlinear effect of herd immunity, we first assume that the transmission matrix β_{ij} is proportional to the matrix C_{ij} of contacts likely to contribute to the disease spread.

To compare the structure of such matrices it is convenient to divide each element by the largest element so that each new element is between 0 and 1. The normalised transmission matrix calculated by Bauch *et al.* for the considered age-classes in Canada can be derived as [120]

$$\tilde{\beta}_{ij}^{(Canada)} = \begin{pmatrix} 1 & 0.24 & 0.26 \\ 0.24 & 0.24 & 0.26 \\ 0.26 & 0.26 & 0.26 \end{pmatrix}$$

On the other hand the normalised matrix of close contacts at home , work and school that lasted at least 15 minutes for the considered age-classes in Belgium [124] is

$$\tilde{C}_{ij}^{(Belgium)} = \begin{pmatrix} 1 & 0.25 & 0.24 \\ 0.25 & 0.68 & 0.23 \\ 0.24 & 0.23 & 0.2 \end{pmatrix}$$

Except for one diagonal component, the two structures are similar. Hence it is reasonable to assume that

$$\beta_{ij}^{(Belgium)} = q \times \tilde{C}_{ij}^{(Belgium)}$$

The factor *q* can be estimated from the effective reproduction number R determined by the analysis of outbreak data. The recursive equation for the growth (decay) of the infectious population is

$$I_{t+1} = R^{\frac{\gamma}{L}} I_t$$

where γ is the inverse of the average infectious period and L the time scale. The associated continuous growth (decay) rate is

$$\lambda = \frac{\gamma}{L}\ln(R)$$

For an average infectious period of two weeks and a half, we have

$$\frac{\gamma}{L} = \frac{52}{2.5}, \quad R = 0.76 \ \ (0.69,0.85) \ \ \Rightarrow \ \ \lambda = -5.71 \ \ (-7.72,-3.63)$$

where 95% confidence intervals are given between brackets. On the other hand, the fraction of infectious individuals in each age-class evolve during an outbreak according to

$$\frac{dI_i}{dt} = S_i \sum_{j=0}^{2} \beta_{ij} I_j - \gamma_i I_i \quad i = 0,1,2$$

neglecting demography and excluding import. The system behaves linearly around its steady state

$$\frac{dI_i}{dt} = \sum_{j=0}^{2} M_{ij} I_j \quad M_{ij} = q S_i^* \tilde{C}_{ij} - \gamma_i \delta_{ij} \quad i = 0,1,2$$

where S_i^* is the steady state value of the fraction of susceptible individuals in age-class *i*. The factor *q* is estimated by equating the largest eigenvalue of the evolution matrix M_{ij} to λ when S_i^* is approximated by $S_i^{(2002)}$, the fraction of susceptible individuals observed in 2002. The result is

$$q = 12.2 \ \ (10.1,14.3)$$

The estimation of the import rates τ_i for ε=95% and $a_V \leq 55$y when non linear effects are taken into account gives

$$\frac{\tau_0}{L} = 0.36\%\text{y}^{-1} \quad 0.17\%\text{y}^{-1} \leq \frac{\tau_0}{L} \leq 0.68\%\text{y}^{-1}$$
$$\frac{\tau_1}{L} = 0\%\text{y}^{-1} \quad 0\%\text{y}^{-1} \leq \frac{\tau_1}{L} \leq 0.05\%\text{y}^{-1}$$
$$\frac{\tau_2}{L} = 0\%\text{y}^{-1} \quad 0\%\text{y}^{-1} \leq \frac{\tau_2}{L} \leq 0.9\%\text{y}^{-1}$$

The lower and upper bounds for τ_i correspond respectively to the smallest and largest decrease (or largest and smallest increase) in S_i between 1993 and 2002 with the largest and smallest value of *q* (that measures the amplitude of the transmission coefficients) according to the 95% confidence intervals. As expected the upper bound for each τ_i calculated from the non linear model is lower than the upper bound for its maximum value calculated from the linear model (obtained by neglecting endogenous transmission). The non linear estimation suggests, in agreement with the linear approximation, that the import rate first decreases and then increases with age. On that basis, we project the observed state in 2002 over 6 years to predict the situation in 2008

$$S_0^{(2008)} = 0.86 \quad (0.79 - 0.89) \qquad R_0^{(2008)} = 0.14 \quad (0.11 - 0.21)$$
$$S_1^{(2008)} = 0.75 \quad (0.71 - 0.79) \qquad R_1^{(2008)} = 0.25 \quad (0.21 - 0.29)$$
$$S_2^{(2008)} = 0.41 \quad (0.35 - 0.45) \qquad R_2^{(2008)} = 0.59 \quad (0.55 - 0.65)$$

Between 2002 and 2008, in agreement with the linear approximation, the predicted trend is a decrease in the fraction of susceptible individuals (increase in the fraction of recovered ones) among young people (first two age-classes) and a more pronounced increase in the fraction of susceptible individuals

(decrease in the fraction of recovered ones) among old people (last age-class). The prediction for the proportion and the number of infected individuals by age group is:

$$i_0^{(2008)} = 4.9 \quad (1.9 - 11) \quad \times 10^{-4} \quad \overset{N_0=1.8\times10^6}{\Rightarrow} \quad I_0^{(2008)} = 880 \quad (340 - 1980)$$
$$i_1^{(2008)} = 8.5 \quad (2.7 - 27) \quad \times 10^{-5} \quad \overset{N_1=2\times10^6}{\Rightarrow} \quad I_1^{(2008)} = 170 \quad (50 - 540)$$
$$i_2^{(2008)} = 3.5 \quad (1.2 - 24) \quad \times 10^{-5} \quad \overset{N_2=6.6\times10^6}{\Rightarrow} \quad I_2^{(2008)} = 230 \quad (80 - 1580)$$

The non linear calculation agrees qualitatively with the linear one but it broadens the uncertainty in the first two age-classes (young people) mainly by decreasing the lower bound for the fraction of susceptible individuals (increasing the upper bound for the fraction of recovered individuals). As a result the maximum numbers of infectious individuals predicted for the first two age-classes are significantly larger. On the other hand the minimum numbers of infectious individuals predicted for the last two age-classes are non zero.

Note that the estimated numbers of infection imply that the cases are underreported by a factor of about 3 for the age groups > 15y, and of about 7 for the age groups 0-15y (see also **table 57**)

Table 57: Model calibration: predicted and reported number of infections and implied underreporting factors

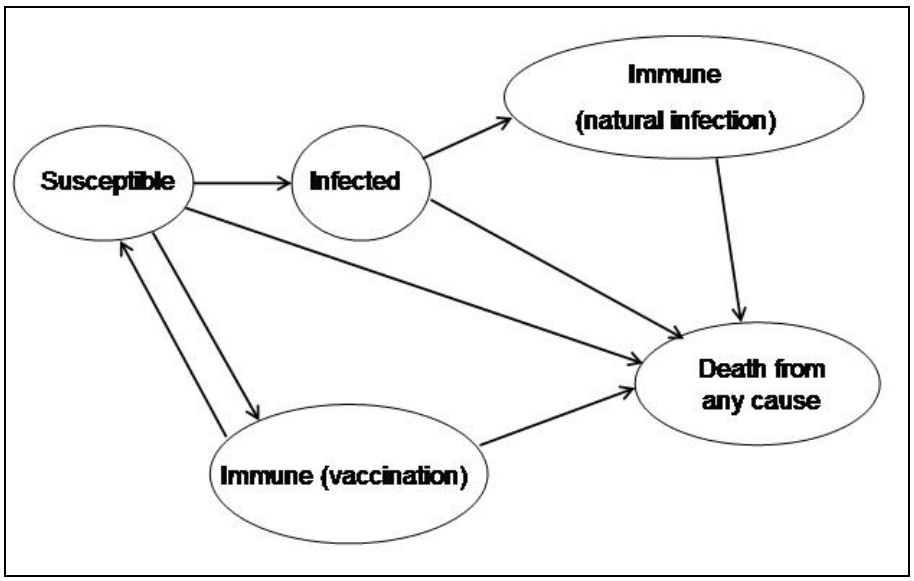
Age group	Modelled population	Infections estimated in dynamic model	mean number of infections reported per year	Implied underreporting factor	hospitalisations
0-15	1,800,455	910	126.7	7.2	29
16-30	1,979,023	230	58.7	3.9	15.8
30+	6,887,388	320	138.3	2.3	15.2
total	10,666,866	1460	323.7	4.5	60

3.1.2.2 Targeted options with negligible impact on general population epidemiology

As discussed above, in order to make model-based analyses of targeted strategies, aimed at groups without a substantial influence on the population epidemiology of hepatitis A in Belgium (health care workers, secondary school teachers), we will use the classic health technology assessment approach of applying a static Markov cohort model.

The simulation model is then a deterministic compartmental static model. Individuals are modelled to progress and/or regress between different relevant disease stages according to their age in years from the average age at entry in the target group in question until death (distinguishing deaths from hepatitis A from other causes).

Figure 26: Basic structure of the static Markov cohort model



Individuals are modelled to transition between the depicted states (**Figure 26**) according to annual age-specific rates, described in section 4.2 below. All states depicted in **figure 26** are reflexive as well as transitive.

The state "Infected" leads to a subroutine calculation (not shown) assigning further health states and unit costs according to age-specific probabilities described in section 2.3.

4 RESULTS

4.1 DISEASE BURDEN

Table 58 shows the disease burden currently estimated for Belgium, as produced by the models using the Belgian epidemiological and resource use data from the various sources discussed above.

The results are shown accounting for the uncertainty in the input parameters, indicating that about 2 to 6 deaths per year occur per year in Belgium, resulting in the loss of 14 to 73 life years, as estimated by the 95% CI in table 56. This burden aggregated in terms of both morbity and mortality translates in the loss of about 400 QALYs per year (ranging from 162 to 677).

Table 58: Estimated current disease burden of hepatitis A in Belgium per year (results from 10,000 simulations)

Name	Mean*	Standard Deviation	Median*	5% Percentile	95% Percentile
symptomatic cases	885.58	52	878	816	979
ambulatory cases	825.43	52	818	754	920
hospitalisations	60.15	6.7	60.0	49.4	71.6
liver transplantations	0.56	0.27	0.52	0.18	1.07
deaths	3.66	1.19	3.54	1.91	5.78
Life-Years lost	35.9	19.5	31.1	14.8	73.6
QALYs lost (morbidity)	18.9	8.5	18.2	5.9	33.4
QALYs lost (total)	54.8	21.4	50.9	28.0	96.0
Direct medical costs (incl prophylaxis in clusters)	311,049	67,003	306,409	207,391	429,355
Indirect costs of morbidity	2,349,655	391,673	2,327,920	1,726,998	3,011,624

Table 58 does not include current vaccination costs financed by individuals and various third parties such as employers and the Fund for Occupational Disease. Based on the 2006 sales figures in section 2.1.2, these can be estimated at €11,525,544 for the purchase of vaccines (of which €1,784,570 and €35,980 for the monovalent HAV vaccines Havrix and Epaxal, respectively, and €9.7 million for the bivalent combined HAV-HBV vaccine Twinrix). Since these figures represent the sales of an estimated 91,609 two or three dose schedules, for which on average at least 1 physician consult is likely to be charged, this implies that in addition Belgians and their insurers currently spend about €1.9 million in costs for administering these vaccines privately (and of which 21516 schedules are for monovalent HAV vaccines, representing estimated administration costs of €463,219). In summary, in addition to the disease burden observed in **table 58**, the total current societal costs of vaccination with the aim to immunise against HAV can be estimated at between €2.3 million (monovalent only) and €13.5 million (both mono and bivalent vaccines) per year. Since it is highly speculative how these costs would evolve (or indeed whether they would remain at this level if no universal program is undertaken), we will ignore in what follows the impact of universal vaccination options on these personal vaccination costs, which are currently greater than the burden represented by cases of hepatitis A as described in **table 58**. Clearly in doing so we are conceptually approaching the analysis of universal strategies in a very conservative manner, possibly already when presenting results over a time span of more than 10 years, when these individual immunisation efforts are likely to start being adapted substantially under the influence of widespread vaccination, and definitely over time spans of 50 years or more (if vaccine induced cellular immunity offers protection over such a long duration, which is currently thought to be the case in the medical literature, see section 1.2.3 above).

4.2 INCREMENTAL EFFECTIVENESS ESTIMATES

We assess the impact of different vaccination strategies by considering the evolution of the infectious population by age-class starting from the most likely situation predicted in 2008 (see section 3.1.1.1 above).

The non linear system of ordinary differential equations is numerically integrated:

1) without additional vaccination;

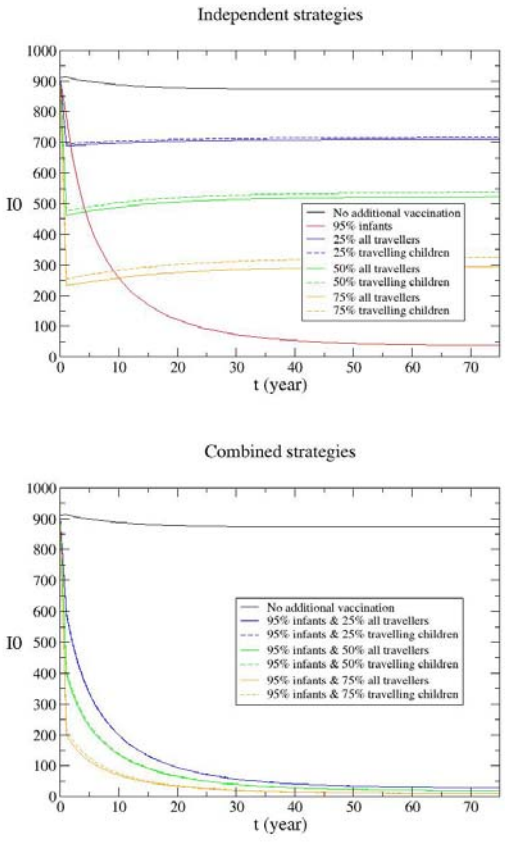
2) vaccinating 95% of infants;

3) reducing all HAV importations by 25%, 50% and 75% or only HAV importations of children (<15y) by 25%, 50% and 75% of travelling only;

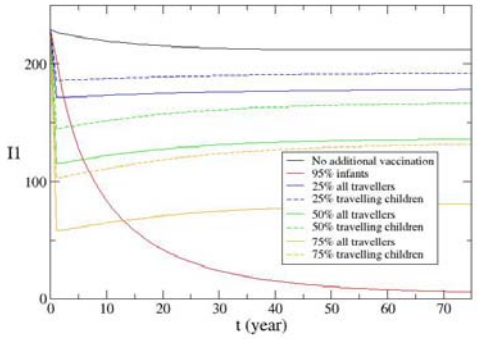
4) combining options 2) and 3).

The evolution curves of the number of infected individuals in the three age-classes for the different additional vaccination scenario are shown in **figure 27**.

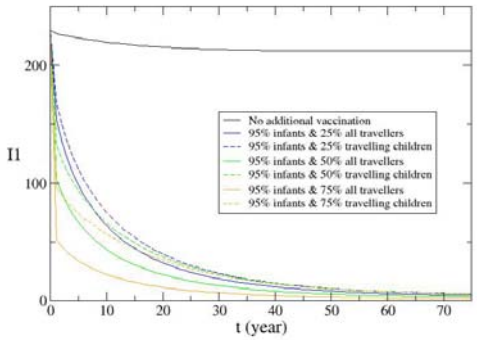
Figure 27: Evolution of the infectious population by age-class for a period of 75 years, corresponding to the average life time, under different vaccination strategies.



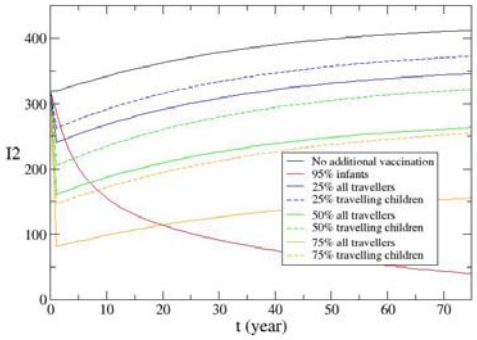
Independent strategies



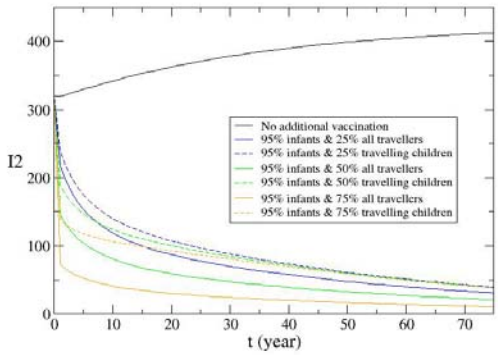
Combined strategies



Independent strategies



Combined strategies



In the absence of more widespread vaccination, the population of infectious individuals slightly decreases in the first two age-classes (young people) and significantly increases in the third age-class (old people). Indeed the fraction of susceptible individuals is predicted to decrease among young people and to increase among old people. In general, vaccinating infants is less effective in the short run but more effective in the long run than vaccinating travellers. Of course, older people experience later the long run effective impact from vaccinating all the infants. Vaccinating only travelling children has obviously less impact than vaccinating all (child and adult) travellers. The difference in impact between the more targeted approach to travel vaccinations is negligible among children (first age-class) but is more substantial among older people. Combining vaccination of infants and travellers has the largest impact both in the short and longer term. The advantage of this combined approach however vanishes after a few decades if only travelling children are vaccinated, rather than both child and adult travellers. We discuss these results in more details below.

Figure 27 shows the decline in the annual number of infections under various scenarios of reduction of HAV transmission in Belgium, either (1) through a reduction of travel importations, for which reductions of infections imported by children (<15y) are distinguished from infections imported by travellers of all ages or (2) by universal vaccination of all infants living in Belgium (at age 1 year), or combinations of (1) qnd (2). Note that not all simulated options are presented here, as only the most relevant for analysis are retained. It can be observed that reductions in travel import have an immediately large impact on the number of infections, and that especially reductions in importations by children contribute to this impact. Furthermore, universal infant vaccination has a larger impact than reducing travel importations from time spans of 5 to 10 years (for reductions of 75% of import by children and by travellers of any age, respectively). Sustained and immediately large reductions can be achieved by combining universal infant vaccination with such large reductions in travel importations.

Figure 28: Annual number of infections over time for the introduction of universal infant vaccination and reductions in importations of hepatitis A infections in year 0 (all ages combined)

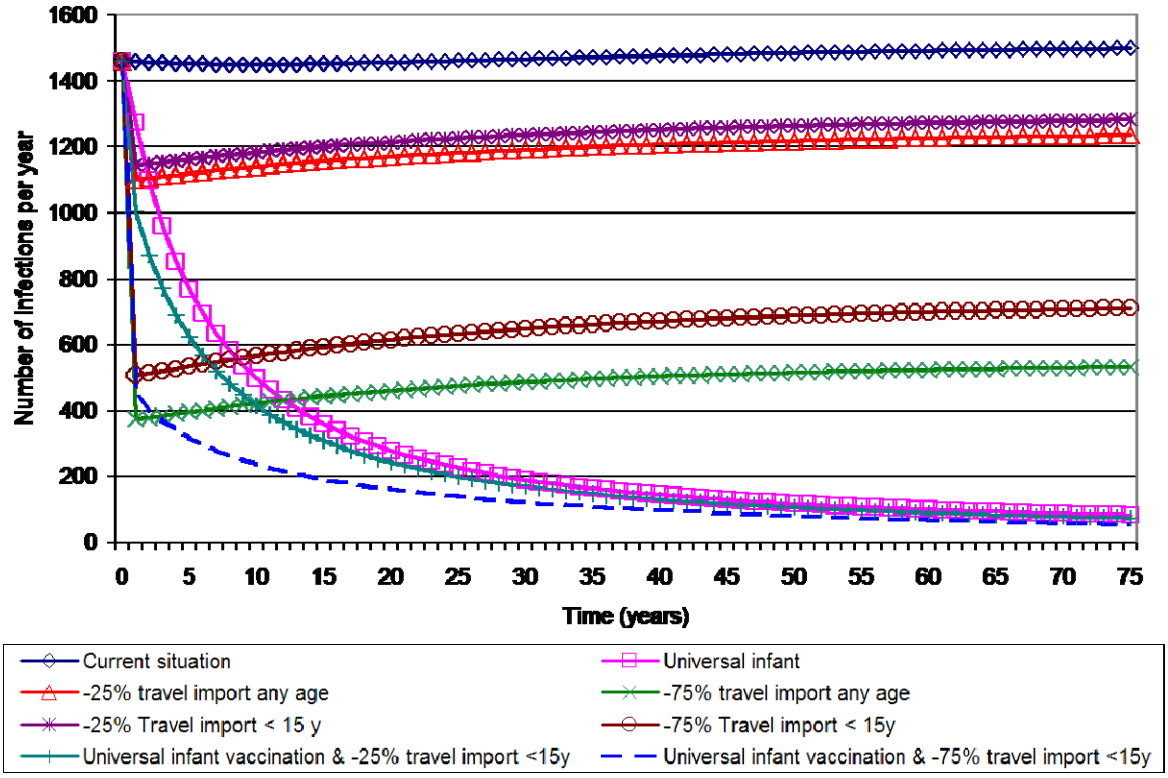


Figure 29: Impact on the number of infections of universal infant vaccination at age 1 year in the various age groups over time

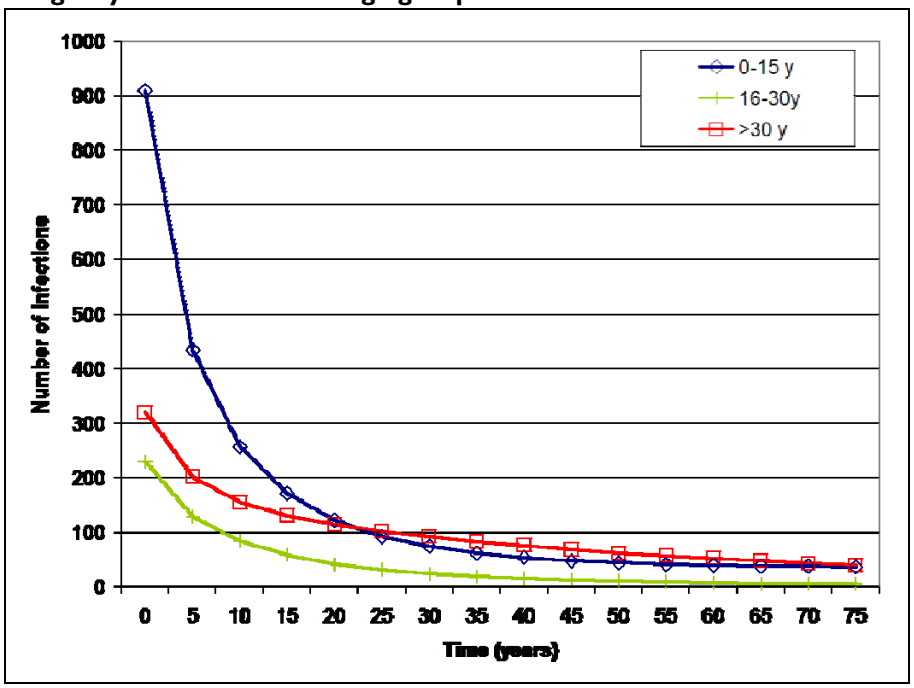
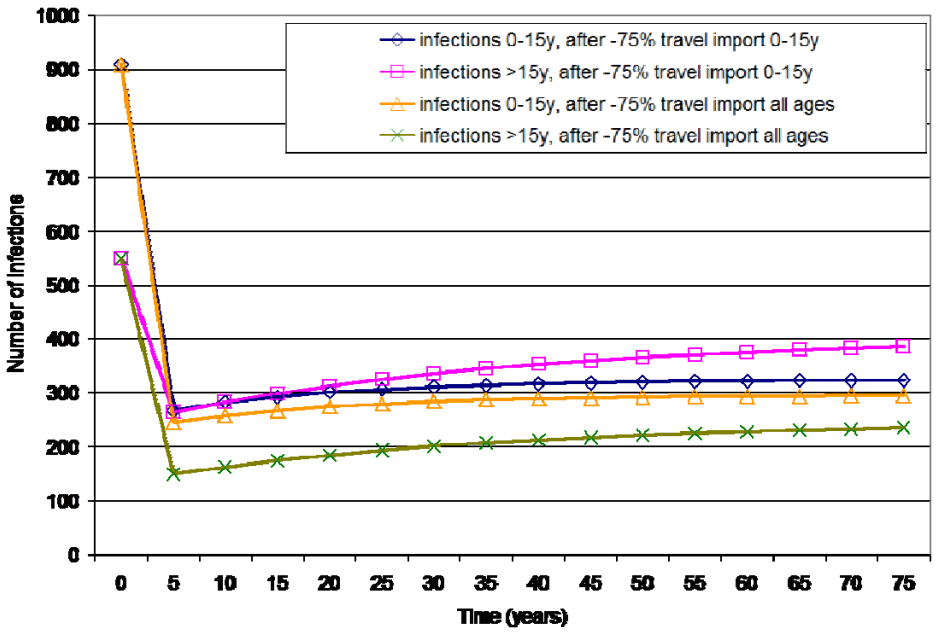


Figure 29 above shows that universal infant vaccination at age 1 year has a gradual impact, particularly at first in the age group 0-15 years of age, in which over a ten year time period the annual number of infections are reduced to less than a third of their current magnitude. The impact in the other age groups is, through herd immunity, also immediate but less dramatic (the number of infections are more than halved over a ten year time period). Note also that after about 10 years the combined number of residual infections in the age groups > 15 y exceed those of the youngest age group.

In **figure 30** below the impact of reducing the travel import by 75% in all travellers and child travellers 0-15 y alone, are shown for the various age groups too. Indicating as shown also above that the importations by children 0-15y are by far the most important ones to reduce.

Figure 30: Impact of reducing the travel import by 75% on the number of infections by age group



Note that the reduction in the force of infection through immunisation will give rise – as expected – to an increase in the average age at infection of residual infections. The predictions in this respect (incorporated in all the analyses), are shown explicitly in **figures 31, 32, 33**.

Figure 31: Changing age distribution of residual infections after introduction of universal infant vaccination at 95% uptake

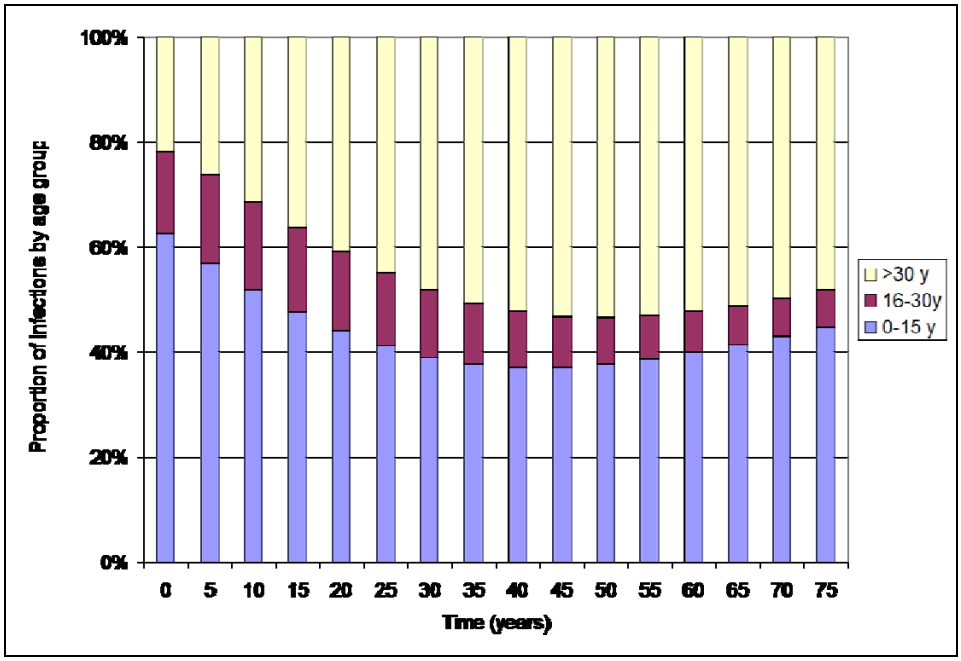


Figure 32: Changing age distribution of residual infections after reducing the importation of infections by children by 75%

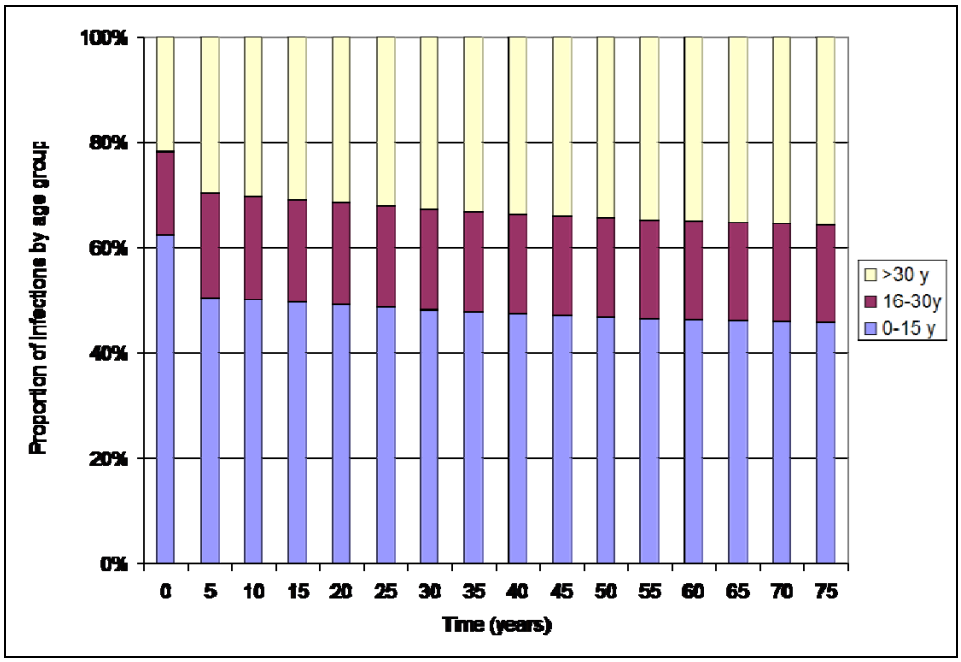
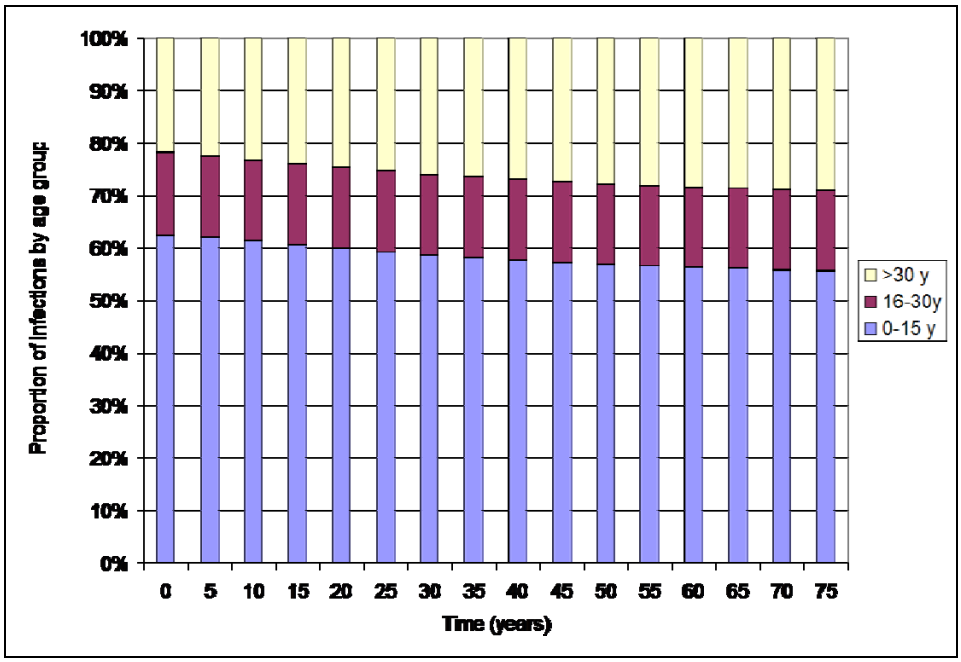


Figure 33: Changing age distribution of residual infections after reducing the importation of infections by people of any age by 75%



4.3 INCREMENTAL COST-EFFECTIVENESS ESTIMATES

4.3.1 Options with a general population impact

Tables 59, 60, 61, 62 present the ICERs for various key options for universal vaccination:

1. Infants 95% vs current: Universal infant vaccination at 95% uptake (and 95% efficacy, ie 90.25% effective uptake) versus the current situation (excluding personal costs of vaccination, see above)
2. TI 75% vs current: Reducing the travel import of HAV infections in 0-15y olds by 75% through the vaccination, at 80% effective uptake (I.e. uptake 84% at 95% efficacy) of immigrant children of Turkish and Morrocon ancestry, aged 1-12y in the first year , and aged 1y only thereafter, versus the current situation
3. Infants 95% vs TI75%: strategy (1) versus (2) above
4. Infants 95% &TI25% vs TI75%: Universal infant vaccination at 95% uptake, asssuming this will simultaneaously reduce the travel import in 0-15y olds by 25% (at no extra cost) versus reducing the travel import of HAV infections in 0-15y olds by 75% through the vaccination, at 80% effective uptake (I.e. uptake 84% at 95% efficacy) of immigrant children of Turkish and Morrocon ancestry

The tables 59, 60, 61, 62 present these results accumulated over time spans of 10 years, 30 years, 50 years and 75 years respectively. Clearly the results are highly dependent on the time span adopted. In view of the current evidence regarding vaccine protection at least a 30 year time span should be taken.

As figures 34a and 34b indicate that the order of magnitude of the ICERs of the options versus no vaccination stabilises after about 30 years, Figure 34b shows a close up of the targeted strategies in figure 34a, since the latter targeted strategies show much lower ICERs over time, and hence can potentially be considered cost-effective. Figure 35 shows the same information using higher discount rates of 5% for both costs and effects. The results are robust to these different discount rates in that the ranking of strategies based on the ICERs remains unaffected over time, though these strategies all become less attractive.

Figures 36 and 37 show the cost-effectiveness acceptability curves for some of the key options, whereas figures 38 and 39 show the sensitivity of the ICERs to changes in vaccination costs (purchasing price and administration costs). Finally table 63 presents an overview of the main results of the probabilistic sensitivity analyses for the costs and QALYs seperately, in addition to the ICER.

These tables and figures indicate that versus the current situation interventions targeting reductions in travel importation would be considered cost-effective. The question remains however, how can we reduce the travel importations by 25 to 75%? Would it be sufficient, as is assumed in these calculations to introduce targeted vaccination of children of Morrocon and Turkish ancestry (2 nd generation) under the age of 13 years (eg, through schools) , followed by annual vaccination of the birth cohort produced by the Morrocon and Turkish communities, and would this be a feasible strategy in Belgium? Above all, would this strategy be effective at reducing HAV importations by children by the modelled rates?

If the answer is yes, then in theory, we could estimate how high at their highest the costs of such an endeavour could be allowed to be before it became less cost-effective than the more effective option of vaccinating all children at age 1 year (that is, before its incremental cost-effectiveness ratio would equal that of universal infant vaccination combined with reducing the travel importations by 75%). Thus it can be estimated that € 856,432 ; € 2,156,356 and €3,672,194 could be spent annually on reducing the travel importations by 25%, 50%, and 75%, respectively, before such spending (if it achieves its goal) would represent less value for money than to vaccinate all Belgian 1 year olds. This is however, adopting a strict governmental perspective, excluding savings from gradual declines in vaccination rates in adults, which are substantial and currently financed from personal or third party resources. These declines are much more likely to occur with a universal vaccination program in all Belgian infants, as opposed to targeted vaccination of Morrocon and Turkish children.

If the answer is no, then we should consider only the universal infant vaccination strategy, and its cost-effectiveness should be assessed versus the next best alternative, i.e. the current situation (in the absence of other viable alternatives). The results indicate that versus the current situation universal infant vaccination would not be considered cost-effective for the Belgian health care system, nor for Belgian society. That is, unless –as indicated in figures 38 and 39 – vaccination costs per fully vaccinated person decrease by 70% (for a societal perspective, including work losses associated with morbidity) or by 90% (for a restricted health care system perspective)

Table 59: Incremental Cost-Effectiveness Ratios (ICERs) after 10 years time span

Direct costs per	Infants 95% vs current	TI 75% vs current	Infants 95% vs TI 75%	Infants 95% & TI 25% vs TI75%
Symptomatic case prevented	33,259	1,434	-67,204	-147,046
Hospitalisation prevented	483,733	20,879	-981,286	-2,152,794
Liver transplantation prevented	52,524,650	2,258,715	-105,322,163	-229,275,307
Death averted	8,932,370	384,842	-18,017,579	-39,371,692
life-year gained	1,080,056	46,730	-2,207,907	-4,868,787
QALY gained	628,869	27,226	- 1,288,209	-2,844,774
Total costs per	**Infants 95% vs current**	**TI 75% vs current**	**Infants 95% vs TI 75%**	**Infants 95% & TI 25% vs TI75%**
Symptomatic case prevented	31,040	-774	- 69,387.02	-149,188
hospitalisation prevented	451,465	-11,265	- 1,013,159	-2,184,150
death averted	49,020,915	-1,218,675	- 108,743,168	-232,614,807
liver transplantation prevented	8,336,523	-207,639	- 18,602,814	-39,945,159
life-year gained	1,008,009	-25,213	- 2,279,623	-4,939,703
QALY gained	586,920	-14,690	-1,330,052	-2,886,209

Note that the negative values indicate that for
- TI75 versus current: cost savings occur from a societal perspective for all time spans (see also tables 60 and 61);
- infants 95% vs TI75%: negative effects occur (i.e. the accumulated incremental effects are smaller for the universal vaccination strategy than for the targeted strategy over this time span).

Table 60: Incremental Cost-Effectiveness Ratios (ICERs) after 30 years time span

Direct costs per	Infants 95% vs current	TI 75% vs current	Infants 95% vs TI 75%	Infants 95% & TI 25% vs TI75%
Symptomatic case prevented	17,384	744	151,419	84,743
Hospitalisation prevented	254,292	10,883	2,220,394	1,240,569
Liver transplantation prevented	27,488,766	1,170,604	250,040,516	136,780,914
Death averted	4,384,855	192,995	31,292,853	19,404,407
life-year gained	545,058	23,879	4,009,957	2,446,804
QALY gained	320,789	14,002	2,419,125	1,457,687
Total costs per	**Infants 95% vs current**	**TI 75% vs current**	**Infants 95% vs TI 75%**	**Infants 95% & TI 25% vs TI75%**
Symptomatic case prevented	15,405	-1,213	149,266.02	82,635
hospitalisation prevented	225,341	-17,744	2,188,828	1,209,703
death averted	24,359,203	-1,908,675	246,485,753	133,377,716
liver transplantation prevented	3,885,645	-314,679	30,847,971	18,921,613
life-year gained	483,004	-38,934	3,952,949	2,385,925
QALY gained	284,267	-22,831	2,384,733	1,421,419

Table 61: Incremental Cost-Effectiveness Ratios (ICERs) after 50 years time span

Direct costs per	Infants 95% vs current	TI 75% vs current	Infants 95% vs TI 75%	Infants 95% & TI 25% vs TI75%
Symptomatic case prevented	13,575	599	55,364	44,711
Hospitalisation prevented	199,467	8,777	821,087	661,148
Liver transplantation prevented	21,470,742	941,490	89,410,945	71,785,248
Death averted	3,282,303	153,259	11,376,491	9,615,441
life-year gained	415,913	19,113	1,504,109	1,256,253
QALY gained	246,607	11,237	913,087	757,641
Total costs per	**Infants 95% vs current**	**TI 75% vs current**	**Infants 95% vs TI 75%**	**Infants 95% & TI 25% vs TI75%**
Symptomatic case prevented	11,795	-1,169	53,544.03	42,862
hospitalisation prevented	173,314	-17,120	794,101	633,809
death averted	18,655,594	-1,836,333	86,472,273	68,816,798
liver transplantation prevented	2,851,942	-298,924	11,002,579	9,217,825
life-year gained	361,380	-37,278	1,454,674	1,204,305
QALY gained	214,273	-21,917	883,076	726,311

Table 62: Incremental Cost-Effectiveness Ratios (ICERs) after 75 years time span

Direct costs per	Infants 95% vs current	TI 75% vs current	Infants 95% vs TI 75%	Infants 95% & TI 25% vs TI75%
Symptomatic case prevented	11,232	513	35,793	31,403
Hospitalisation prevented	165,698	7,522	535,373	468,285
Liver transplantation prevented	17,763,103	805,543	57,532,466	50,312,474
Death averted	2,620,157	130,425	7,021,440	6,374,737
life-year gained	337,438	16,328	952,654	856,237
QALY gained	201,353	9,611	583,753	521,948
Total costs per	**Infants 95% vs current**	**TI 75% vs current**	**Infants 95% vs TI 75%**	**Infants 95% & TI 25% vs TI75%**
Symptomatic case prevented	9,647	-1,078	34,222.34	29,791
hospitalisation prevented	142,318	-15,810	511,882	444,251
death averted	15,256,782	-1,693,089	55,008,114	47,730,236
liver transplantation prevented	2,250,461	-274,127	6,713,361	6,047,560
life-year gained	289,826	-34,317	910,854	812,291
QALY gained	172,942	-20,201	558,140	495,160

Figure 34a: Direct costs per QALY gained for various universal options versus no vaccination (baseline discounting, i.e. 3% costs, 1.5% effects)

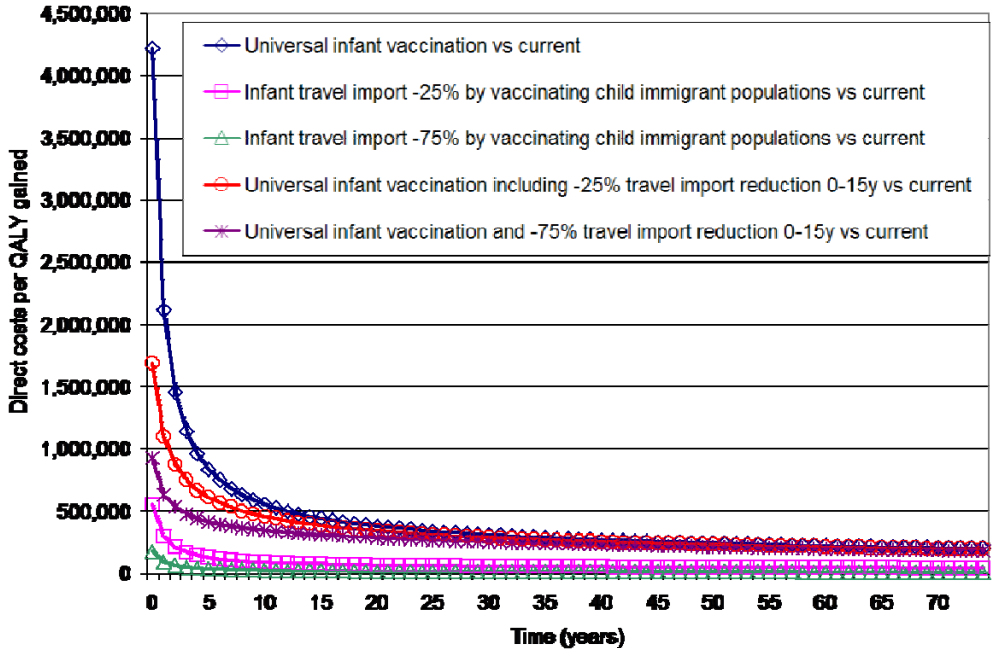


Figure 34b: Direct costs per QALY gained for targeted options versus no vaccination (baseline discounting, i.e. 3% costs, 1.5% effects)

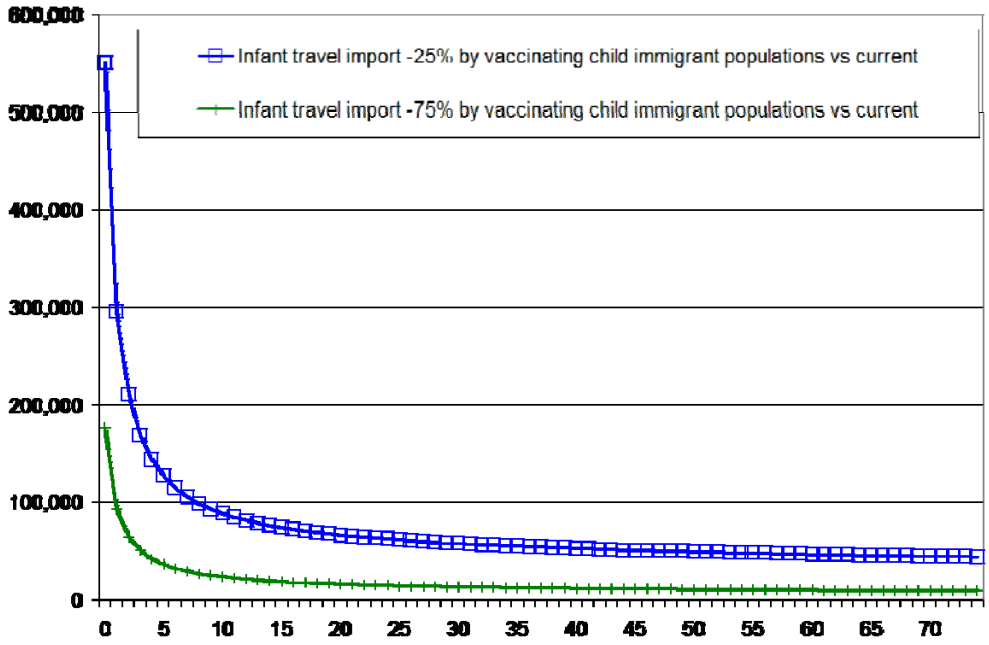


Figure 35: Direct costs per QALY gained for various universal options versus no vaccination (5% costs, 5% effects)

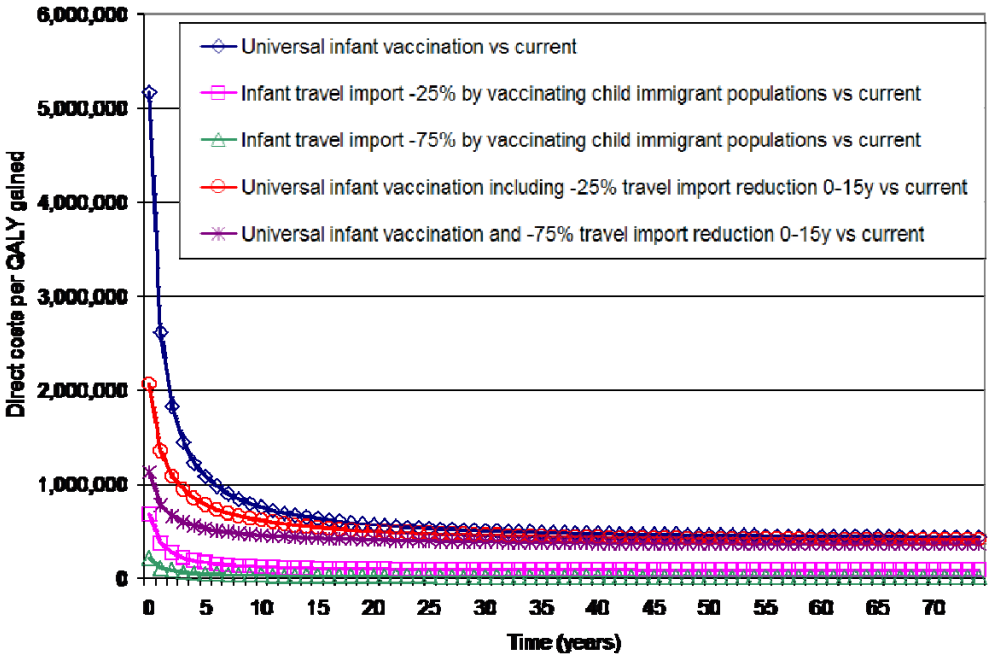


Figure 36: Cost-effectiveness acceptability curves for key options of targeted vaccination versus various strategies of reference, results for a 50 year time span

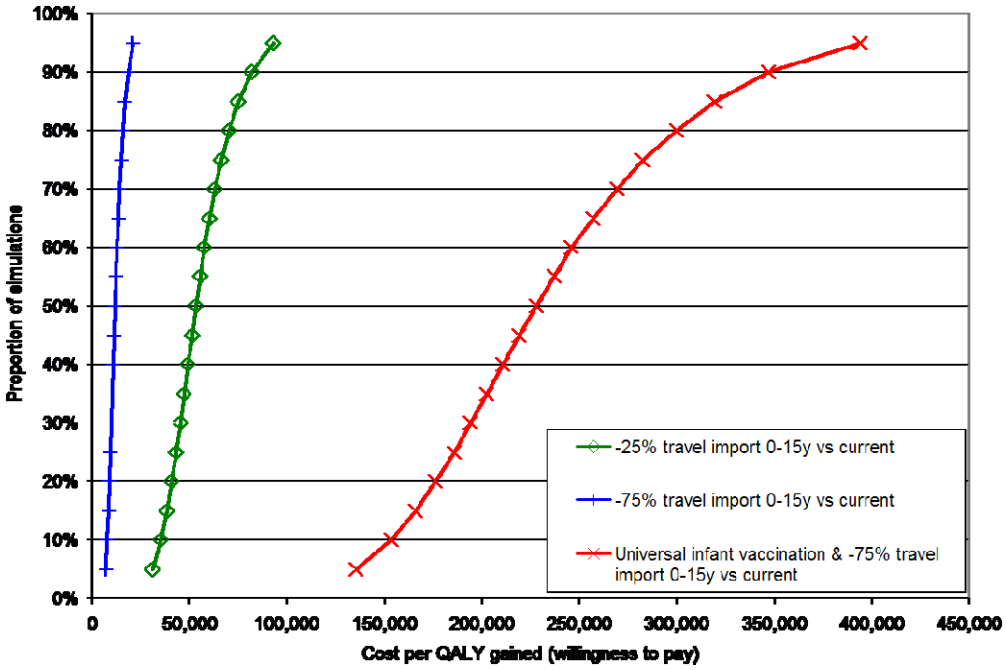


Figure 37: Cost-effectiveness acceptability curves for key options of universal vaccination versus various strategies of reference, results for a 50 year time span

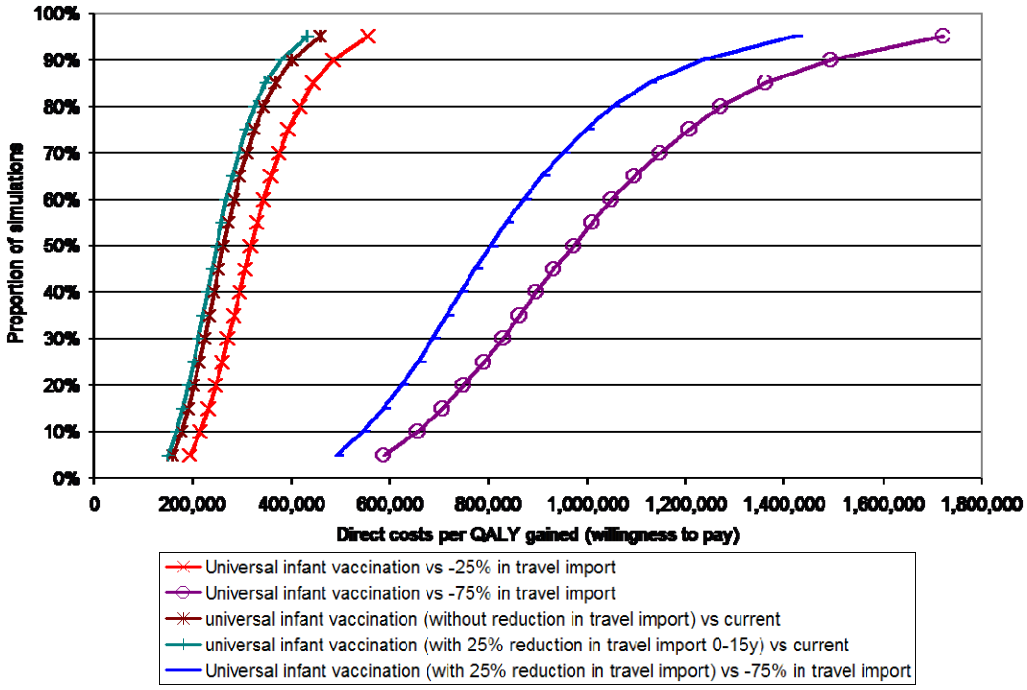


Table 63: Summary table of results from probabilistic sensitivity analyses (5000 simulations) Median (95% CrI) of incremental direct costs , QALYs gained and Incremental direct costs per QALY gained for key options of HAV vaccination.

	Incremental direct costs per QALY gained	Incremental direct costs	QALYs gained
universal infant vaccination (without reduction in travel import) vs current situation	261,519 (155,923-452,295)	303,290,400 (301,163,000-305,024,100)	1,171 (677-1,964)
Universal infant vaccination (with 25% reduction in travel import 0-15y) vs current situation	247,105 (147,300-427,367)	302,932,300 (300,669,600-304,780,600)	1,231 (711-2,064)
-25% travel import 0-15y through vaccination of Turkish and Morrocon immigrants (1-12y of age) vs current situation	52,984 (31,038-92,332)	12,978,440 (12,484,570-13,377,110)	244 (140-417)
-75% travel import 0-15y through vaccination of Turkish and Morrocon immigrants (1-12y of age) vs current situation	11,607 (6,641-20,503)	9,977,214 (8,277,071-11,344,070)	859 (494-1,457)
Universal infant vaccination vs -75% travel import through vaccination of Turkish and Morrocon immigrants (1-12y of age)	968,743 (585,190-1,750,244)	293,314,000 (292,844,800-293,697,600)	310 (172-514)

Figures 38 and 39 show the sensitivity of the results to declines in the vaccination costs per course.

Figure 38: Influence of changes in vaccination costs on the estimated total costs per QALY gained

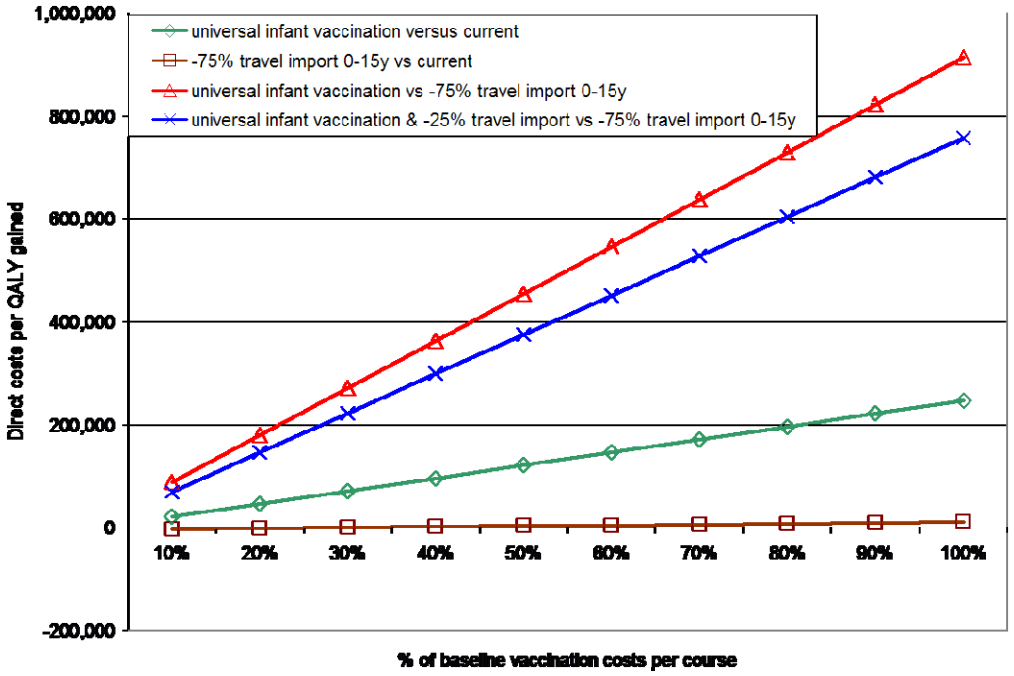
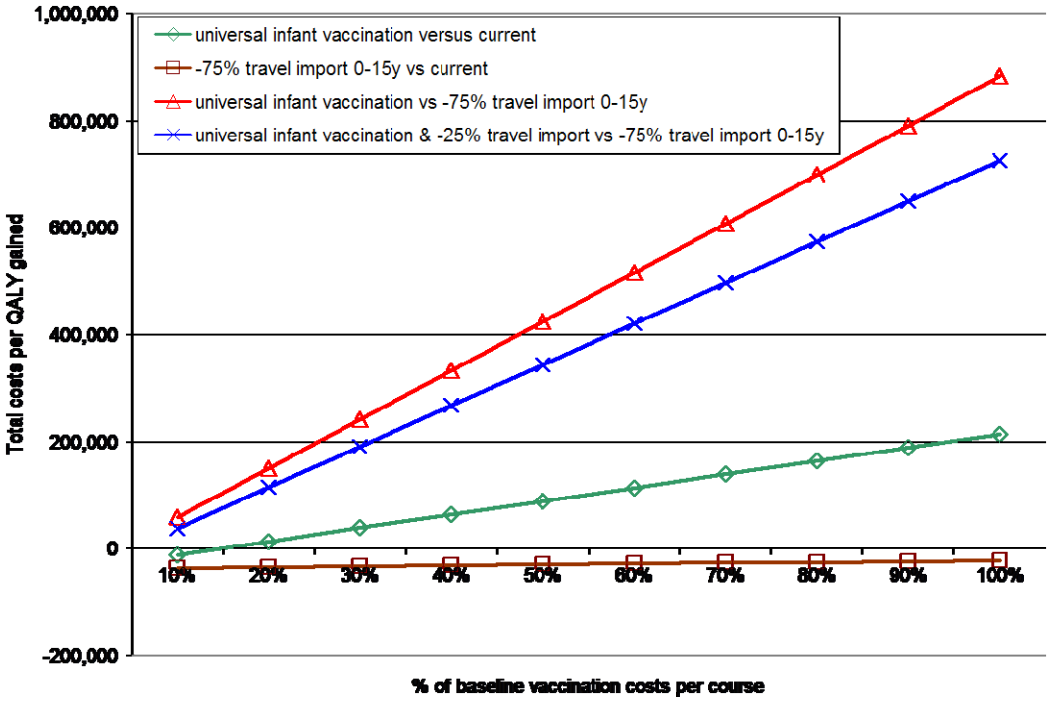


Figure 39: Influence of changes in vaccination costs on the estimated direct costs per QALY gained



4.3.2 Targeted options with an impact in risk groups only

In this section the results are reported for vaccinating adults in general, or a target group at increased risk of infection (eg through occupation), without making a nonlinear contribution to the spread of infection. In these simulations adult groups are targeted at the age of entry into the occupational hazard group, at the start of their career, set here at age 20 years.

Table 64: Incremental Cost-Effectiveness Ratios from 10,000 simulations

	Vaccinate vs. Do nothing				Screen and Vaccinate vs. Do nothing				Vaccinate vs. Screen and Vaccinate			
	Mean	Median	Lower 90% range	Upper 90% range	Mean	Median	Lower 90% range	Upper 90% range	Mean	Median	Lower 90% range	Upper 90% range
HEALTH CARE PERSPECTIVE												
Cost/QALY gained	202,246 €	185,821 €	114,217 €	341,331 €	239,683 €	221,493 €	136,380 €	405,442 €	125,411 €	115,060 €	41,224 €	262,095 €
Cost/infection saved	36,036 €	35,283 €	30,979 €	42,356 €	42,791 €	42,008 €	37,268 €	49,849 €	21,773 €	22,611 €	8,749 €	37,725 €
Cost/hosp saved	1,155,552 €	1,115,656 €	859,141 €	1,535,493 €	1,370,292 €	1,331,441 €	1,026,579 €	1,819,873 €	708,731 €	702,409 €	267,549 €	1,275,805 €
Cost/life year saved	231,713 €	208,927 €	123,837 €	406,806 €	274,541 €	249,141 €	147,503 €	484,857 €	144,217 €	129,303 €	45,506 €	311,549 €
Cost/death averted	5,406,612 €	4,867,652 €	2,883,916 €	9,472,881 €	6,406,786 €	5,808,945 €	3,432,995 €	11,341,820 €	3,363,877 €	3,013,381 €	1,066,462 €	7,293,356 €
SOCIETY PERSPECTIVE												
Cost/QALY gained	199,418 €	183,200 €	112,697 €	336,116 €	236,855 €	218,965 €	134,580 €	400,398 €	122,582 €	112,419 €	38,959 €	258,380 €
Cost/infection saved	35,533 €	34,766 €	30,435 €	41,838 €	42,287 €	41,489 €	36,733 €	49,387 €	21,270 €	22,147 €	8,235 €	37,222 €
Cost/hosp saved	1,139,438 €	1,100,103 €	844,746 €	1,513,939 €	1,354,179 €	1,315,288 €	1,014,197 €	1,802,478 €	692,617 €	686,977 €	252,284 €	1,259,217 €
Cost/life year saved	228,471 €	206,162 €	122,028 €	401,124 €	271,299 €	245,898 €	145,503 €	479,646 €	140,974 €	126,417 €	43,166 €	306,603 €
Cost/death averted	5,330,945 €	4,802,183 €	2,841,201 €	9,349,471 €	6,331,118 €	5,738,305 €	3,383,881 €	11,212,770 €	3,288,209 €	2,944,386 €	1,009,088 €	7,172,879 €

Table 64 shows that both strategies, vaccinating cohorts of specific professional profiles or screening and vaccinating susceptibles, are unlikely to be judged cost-effective. Vaccinating the entire cohort however is a more efficient use of the health care budget than first screening for antibodies and then vaccinating the susceptibles.

There is only a small difference between the societal and the health care payer perspective. The total weight of indirect costs in the total costs remains small compared to the costs of the health care intervention.

Figure 40: Incremental Cost-effectiveness Ratios (ICER's) for three strategies and two perspectives for an increasing time span (0-20 years after vaccination) (results from 10,000 simulations)

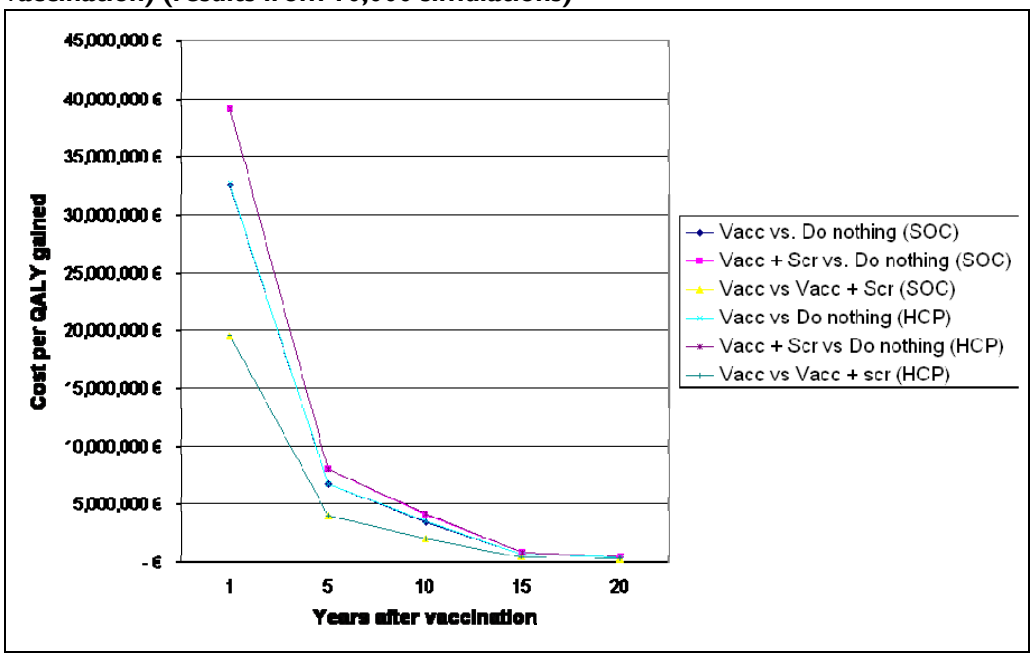
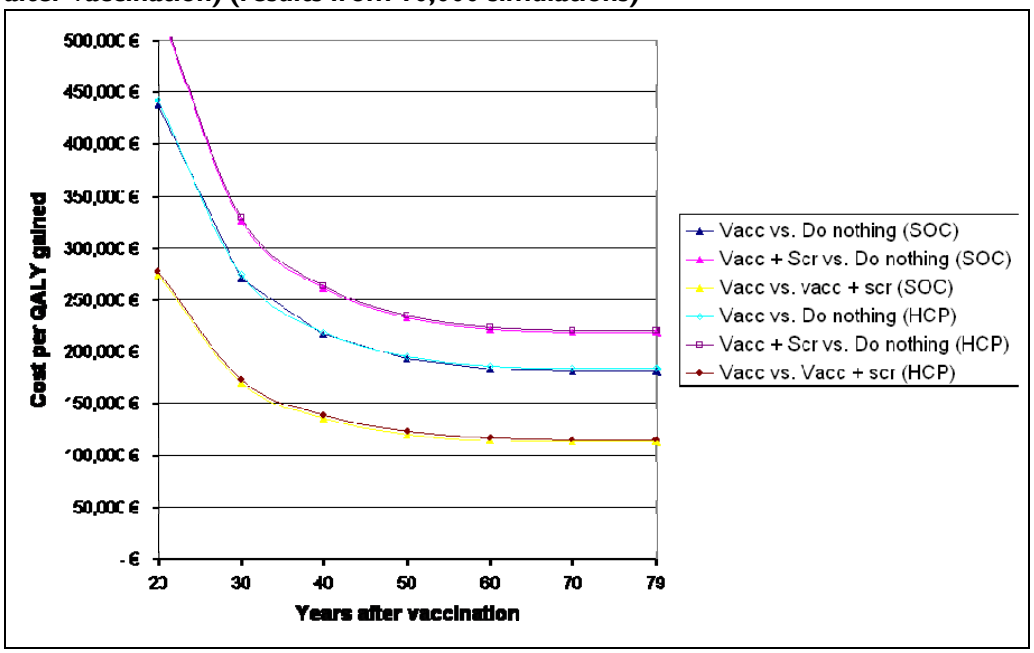


Figure 41: Incremental Cost-effectiveness Ratios (ICER's) for three strategies and two perspectives for an increasing time span (20-80 years after vaccination) (results from 10,000 simulations)



Figures 40 and 41 show the evolution of the cost-effectiveness ratio over time. The first figure shows the first 20 years, the second the evolution for the next 60 years.

Because of the small difference between the societal and the health care payer perspective the curves lie very close to one another. The ICER's start stabilizing at about 50 years after the vaccine administration.

These figures also indicate the cost-effectiveness if the duration of vaccine induced protection would be limited in time. For the rest of this subanalysis a time span of 80 years after vaccination is assumed.

Figure 42: Cost-effectiveness acceptability curves (results from 10,000 simulations)

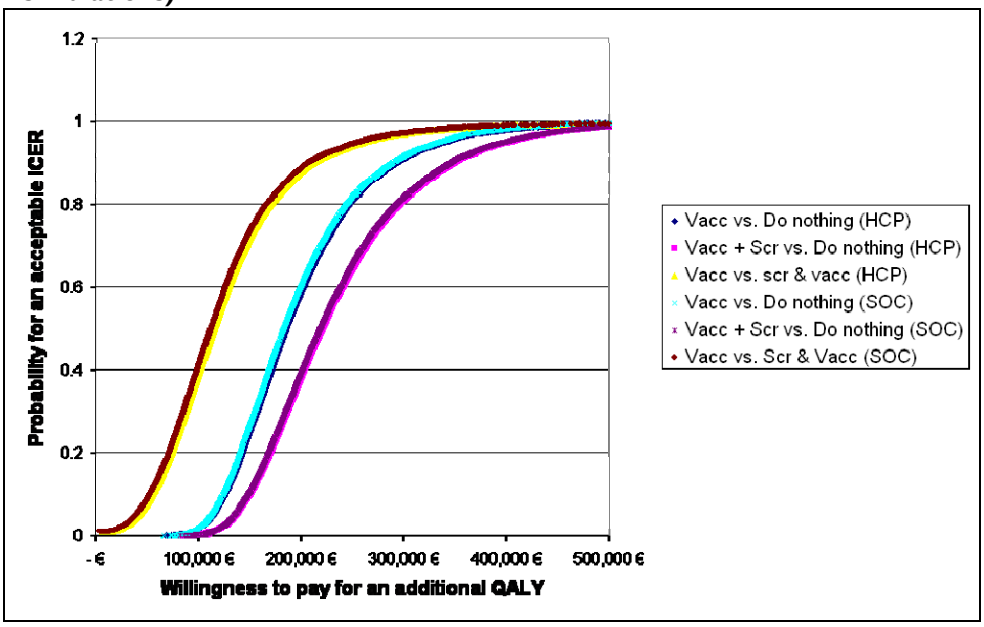


Figure 42 shows the cost-effectiveness acceptability curves for all strategies and perspectives. For a willingness to pay of 35,000 € per QALY, the probability that our analysis produced an ICER versus no vaccination that is equal to this threshold is zero. A 50% probability that the cost-effectiveness ratio will be acceptable requires for vaccination versus do nothing a willingness to pay of 180,000€ per QALY. Screening and vaccination versus do nothing requires 220,000 € as threshold in order to make an economically justified decision in 50% of the scenarios.

Table 65 shows the results from the sensitivity analyses for a number of potentially influential parameters. Since the results for the societal perspective are very similar, only the health care payer perspective is adopted. Although the impact of the discount rate is substantial, in none of the scenarios the intervention becomes cost-effective. The results are insensitive to changes in the cost of liver transplantations and the quality of life and the days of illness associated with this event. If we use the estimated number of deaths from the MKG-data, the alternative for the certificates we used, the results become more cost-ineffective.

For this analysis the force of infection that we assumed was the same as the one for the general population. For some professional subgroups (health care workers, primary school teachers,…) the incidence however may be higher. If the force of infection in the specific subgroup is during their professional career between 4 and 5 times (i.e. between ages 20 and 65 years) as high as in the general population, then vaccinating becomes a cost-effective measure (given a threshold willingness to pay of 35,000€). This is also depicted in the figures 43 and 44.

The total cost of the vaccine is a major determinant in this analysis. If the total cost of vaccination, i. e. the vaccine price plus the cost of administration, can be reduced to 20 % of its baseline value, HAV vaccination might be judged as cost-effective. For the strategy with screening to become cost-effective the vaccine cost must be lowered to 20% and the screen test to 10% of the current cost.

Table 65: Univariate sensitivity analyses of costs per QALY for three strategies from a health care payer perspective for a range of potentially influential parameters (discount rates, livertransplants, deaths and force of infection)

	Vacc vs. Do Nothing				Screen + vacc vs. Do Nothing				Vacc vs. Screen + Vacc			
	Mean	Median	Lower 90%	Upper 90%	Mean	Median	Lower 90%	Upper 90%	Mean	Median	Lower 90%	Upper 90%
Basecase	202,246 €	185,821 €	114,217 €	341,331 €	239,683 €	221,493 €	136,380 €	405,442 €	125,411 €	115,060 €	41,224 €	262,095 €
Discount rates												
0% costs 0% effects	105,170 €	97,243 €	56,805 €	181,775 €	126,006 €	116,379 €	74,764 €	210,434 €	76,073 €	60,749 €	23,611 €	141,342 €
3% costs , 0 % effects	107,145 €	100,182 €	57,422 €	169,808 €	127,710 €	123,304 €	69,980 €	197,436 €	84,649 €	59,850 €	27,573 €	118,867 €
3% costs 3% effects	357,953 €	322,603 €	199,721 €	655,714 €	424,676 €	398,628 €	235,406 €	728,681 €	217,934 €	200,010 €	56,867 €	505,222 €
5% costs, 5% effects	699,516 €	652,033 €	370,193 €	1,180,921 €	835,229 €	763,167 €	445,416 €	1,445,119 €	480,513 €	393,493 €	171,236 €	910,164 €
Livertransplants												
Cost LT *100	184,350 €	171,697 €	104,851 €	294,073 €	222,930 €	198,779 €	130,134 €	379,192 €	116,553 €	97,180 €	24,374 €	267,432 €
QOL LT /100	201,719 €	184,316 €	104,007 €	362,220 €	240,952 €	220,905 €	127,358 €	400,200 €	128,777 €	119,621 €	43,940 €	209,533 €
days ill *100	162,803 €	151,730 €	94,982 €	253,985 €	194,278 €	180,264 €	120,644 €	295,345 €	103,017 €	91,300 €	32,407 €	179,329 €
Deaths (MKG-data)	531,115 €	442,119 €	204,268 €	1,098,440 €	625,103 €	523,315 €	249,884 €	1,294,534 €	335,039 €	272,928 €	97,238 €	700,426 €
Force of Infection scaling factor												
*2	98,778 €	89,818 €	57,367 €	179,293 €	117,789 €	111,695 €	69,920 €	211,564 €	60,777 €	59,388 €	15,339 €	127,504 €
*3	65,320 €	60,099 €	36,965 €	115,907 €	77,849 €	71,355 €	43,395 €	126,685 €	43,316 €	35,749 €	14,417 €	80,594 €
*4	48,417 €	43,724 €	29,080 €	77,609 €	58,506 €	51,985 €	34,869 €	106,011 €	29,587 €	24,233 €	6,513 €	56,650 €
*5	37,444 €	35,471 €	22,283 €	59,243 €	45,193 €	43,046 €	27,237 €	71,603 €	23,685 €	20,823 €	6,135 €	48,944 €
*6	31,406 €	30,658 €	16,641 €	47,815 €	37,694 €	35,581 €	22,009 €	59,180 €	16,978 €	18,219 €	2,859 €	33,573 €
*7	26,489 €	25,201 €	15,368 €	47,935 €	32,403 €	29,896 €	18,293 €	60,068 €	16,397 €	15,008 €	2,535 €	28,131 €

Table 66: Univariate and bivariate sensitivity analysis of costs per QALY for three strategies from a health care payer perspective for a range of potentially influential parameters (vaccine price and screen test price). Results from 10,000 simulations.

	Vaccinate vs Do Nothing				Screen and Vacc vs. Do Nothing				Vacc vs. Screen and vacc			
	Mean	Median	Lower 90%	Upper 90%	Mean	Median	Lower 90%	Upper 90%	Mean	Median	Lower 90%	Upper 90%
Basecase	202,246 €	185,821 €	114,217 €	341,331 €	239,683 €	221,493 €	136,380 €	405,442 €	125,411 €	115,060 €	41,224 €	262,095 €
Total Vaccine costs												
10%	18,525 €	17,655 €	11,423 €	28,357 €	82,322 €	75,527 €	52,620 €	129,372 €	- 117,507 €	-88,904 €	- 295,336 €	-37,829 €
20%	39,036 €	34,933 €	22,274 €	66,647 €	99,888 €	89,254 €	57,046 €	167,939 €	- 878,035 €	- 64,089 €	- 229,239 €	-17,060 €
30%	59,525 €	55,019 €	34,690 €	115,932 €	117,573 €	106,309 €	68,398 €	204,838 €	- 60,743 €	- 48,840 €	-168,678 €	- 1,899 €
Total Vaccine costs screentest 10 %												
10%	18,902 €	16,962 €	10,877 €	37,990 €	23,115 €	20,526 €	12,945 €	47,758 €	11,388 €	10,804 €	1,950 €	20,323 €
20%	38,811 €	36,499 €	21,396 €	59,744 €	39,625 €	38,633 €	22,005 €	61,215 €	39,938 €	35,819 €	19,724 €	63,129 €
30%	58,855 €	55,530 €	33,252 €	95,425 €	56,911 €	52,524 €	32,254 €	92,123 €	56,212 €	57,720 €	32,336 €	121,844 €

Table 67: Univariate sensitivity analysis of costs per LY for three strategies from a health care payer perspective for a range of potentially influential parameters (discount rates, livertransplants, deaths and force of infection)

	Vacc vs. Do Nothing				Screen + vacc vs. Do Nothing				Vacc vs. Screen + Vacc			
	Mean	Median	Lower 90%	Upper 90%	Mean	Median	Lower 90%	Upper 90%	Mean	Median	Lower 90%	Upper 90%
Basecase	231,713 €	208,927 €	123,837 €	406,806 €	274,541 €	249,141 €	147,503 €	484,857 €	144,217 €	129,303 €	45,506 €	311,549 €
Discount rates												
0% costs 0% effects	116,869 €	105,899 €	58,950 €	217,619 €	140,058 €	124,925 €	81,402 €	257,206 €	84,582 €	67,640 €	25,639 €	172,077 €
3% costs , 0 % effects	118,110 €	111,011 €	61,725 €	196,505 €	140,800 €	133,330 €	75,347 €	230,075 €	91,883 €	70,842 €	29,524 €	131,621 €
3% costs 3% effects	426,946 €	383,420 €	227,582 €	717,296 €	506,040 €	463,357 €	270,348 €	908,032 €	259,943 €	224,060 €	71,764 €	646,688 €
5% costs, 5% effects	889,157 €	840,162 €	426,365 €	1,395,924 €	1,060,962 €	993,081 €	511,997 €	1,706,920 €	615,340 €	490,312 €	208,059 €	1,139,388 €
Livertransplants												
Cost LT *100	208,534 €	187,674 €	110,927 €	363,891 €	251,764 €	218,856 €	141,850 €	444,928 €	132,577 €	107,755 €	30,174 €	292,812 €
QOL LT /100	232,088 €	208,039 €	111,403 €	425,496 €	277,585 €	250,546 €	136,414 €	521,614 €	148,335 €	133,029 €	45,774 €	269,121 €
days ill *100	228,905 €	214,792 €	125,218 €	372,549 €	273,604 €	259,538 €	154,689 €	444,254 €	143,599 €	125,099 €	56,534 €	259,312 €
Deaths (MKG-data)	839,211 €	581,706 €	234,734 €	2,148,657 €	988,035 €	683,914 €	292,034 €	2,485,207 €	519,046 €	390,121 €	115,999 €	1,530,314 €
Force of Infection scaling factor												
*2	113,834 €	105,145 €	62,048 €	226,824 €	135,472 €	123,893 €	74,156 €	248,533 €	70,252 €	64,784 €	17,619 €	144,131 €
*3	76,116 €	66,483 €	40,698 €	124,877 €	90,631 €	79,668 €	46,683 €	151,967 €	50,702 €	40,843 €	14,994 €	99,510 €
*4	55,029 €	50,458 €	32,642 €	89,262 €	66,409 €	59,983 €	39,044 €	107,408 €	33,772 €	27,796 €	7,513 €	71,695 €
*5	42,922 €	40,351 €	23,724 €	68,798 €	51,854 €	48,801 €	29,561 €	82,851 €	27,157 €	24,172 €	6,605 €	58,270 €
*6	36,204 €	33,936 €	18,554 €	59,641 €	43,359 €	40,215 €	23,107 €	69,951 €	19,841 €	20,601 €	3,357 €	38,368 €
*7	30,320 €	28,142 €	17,251 €	53,861 €	37,150 €	32,694 €	20,595 €	70,677 €	18,677 €	16,596 €	2,854 €	36,528 €

Table 68: Univariate and bivariate sensitivity analysis of costs per LY for three strategies from a health care payer perspective for a range of potentially influential parameters (vaccine price and screen test price). Results from 10,000 simulations.

	Vaccinate vs Do Nothing				Screen and Vacc vs. Do Nothing				Vacc vs. Screen and vacc			
	Mean	Median	Lower 90%	Upper 90%	Mean	Median	Lower 90%	Upper 90%	Mean	Median	Lower 90%	Upper 90%
Basecase	231,713 €	208,927 €	123,837 €	406,806 €	274,541 €	249,141 €	147,503 €	484,857 €	144,217 €	129,303 €	45,506 €	311,549 €
Total Vaccine costs												
10%	21,371 €	20,109 €	12,466 €	37,261 €	94,723 €	84,852 €	58,159 €	174,326 €	- 100,798 €	- 80,510 €	- 175,328 €	- 44,604 €
20%	44,982 €	39,771 €	24,473 €	78,715 €	115,206 €	101,931 €	63,455 €	186,685 €	- 1,108,344 €	- 70,744 €	- 259,669 €	-19,454 €
30%	68,502 €	61,067 €	36,383 €	118,163 €	135,108 €	120,712 €	69,011 €	221,288 €	- 70,361 €	- 51,414 €	- 238,526 €	- 2,264 €
Total Vaccine costs screentest 10 %												
10%	21,628 €	19,872 €	11,854 €	39,265 €	26,398 €	23,241 €	14,070 €	51,843 €	12,965 €	11,879 €	2,222 €	25,041 €
20%	44,151 €	43,524 €	24,020 €	71,591 €	45,110 €	42,616 €	24,747 €	71,812 €	45,216 €	39,213 €	21,713 €	81,644 €
30%	67,391 €	62,013 €	37,064 €	112,600 €	65,129 €	59,286 €	35,633 €	110,129 €	65,504 €	60,706 €	36,536 €	144,595 €

Figure 43: Incremental direct costs per QALY gained from a health care payer perspective for the baseline force of infection multiplied by a factor from 1 to 7. (Results from 10,000 simulations)

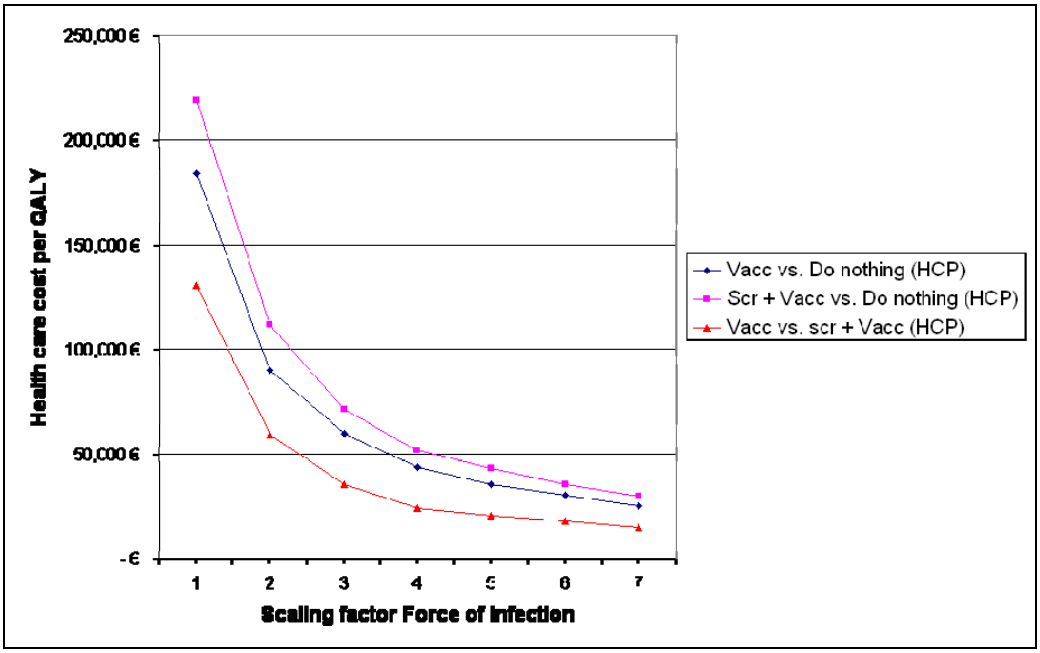


Figure 44: Incremental costs per LY from a health care payer perspective for a force of infection multiplied by a factor from 1 to 7. (Results from 10,000 simulations)

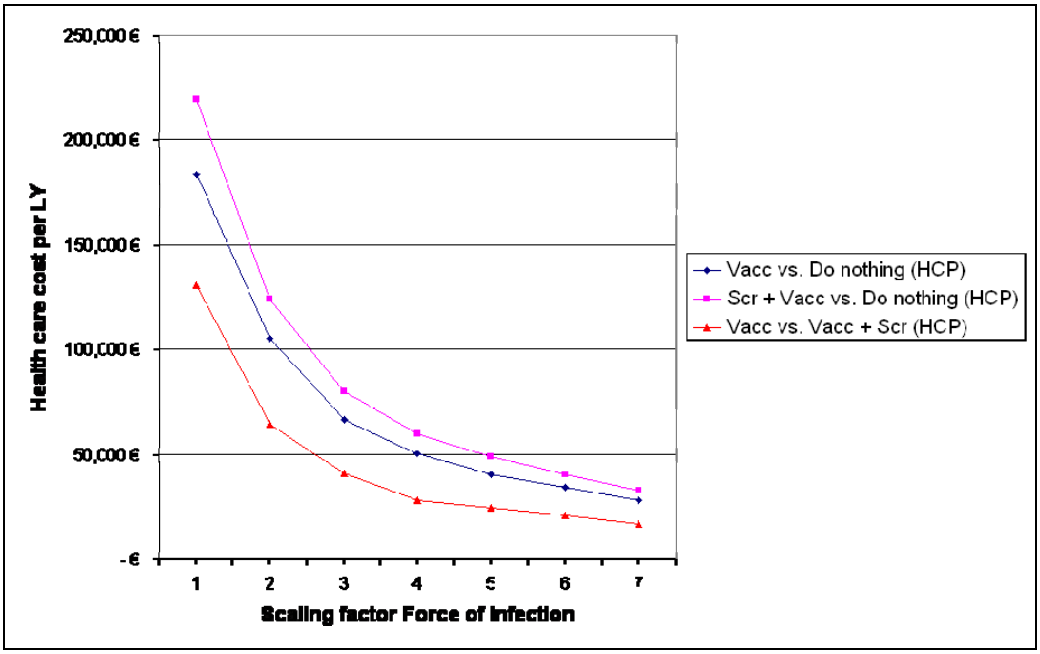
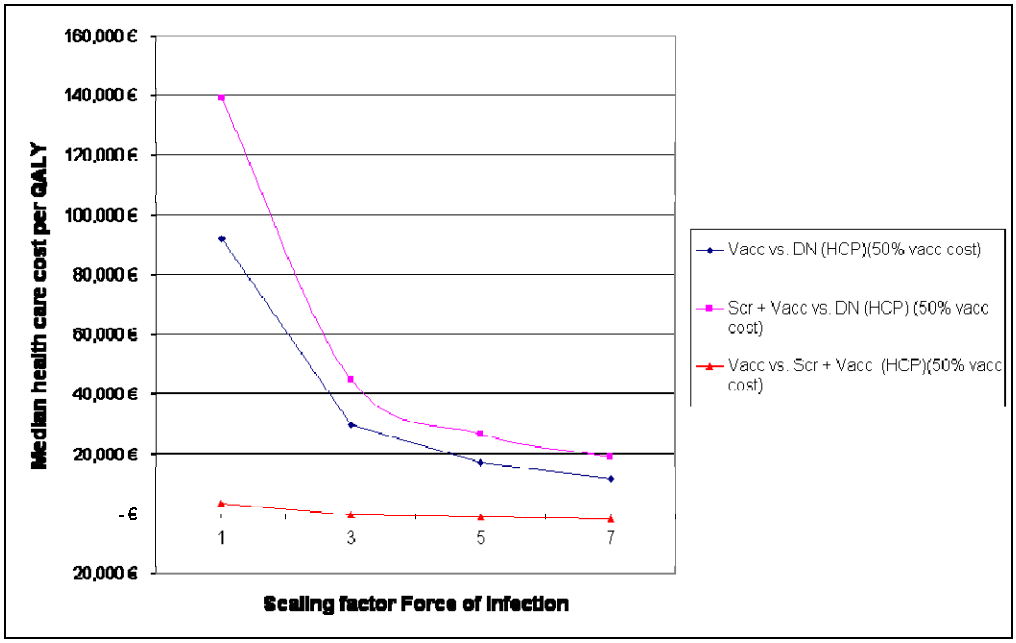


Figure 45: ICER's from a health care payer perspective for a force of infection multiplied by a factor from 1 to 7 and 50% of the vaccine cost . (Results from 10,000 simulations



With a vaccine cost of 50 % of the current value a professional subgroup needs to be faced with a risk that is nearly 3 times as high as the force of infection in the general population in order for their vaccination to become cost-effective. Screening and vaccination becomes interesting when the force of infection is 4 times as high.

Figure 46: ICER's in QALY's for different percentages of price of vaccine and screentest

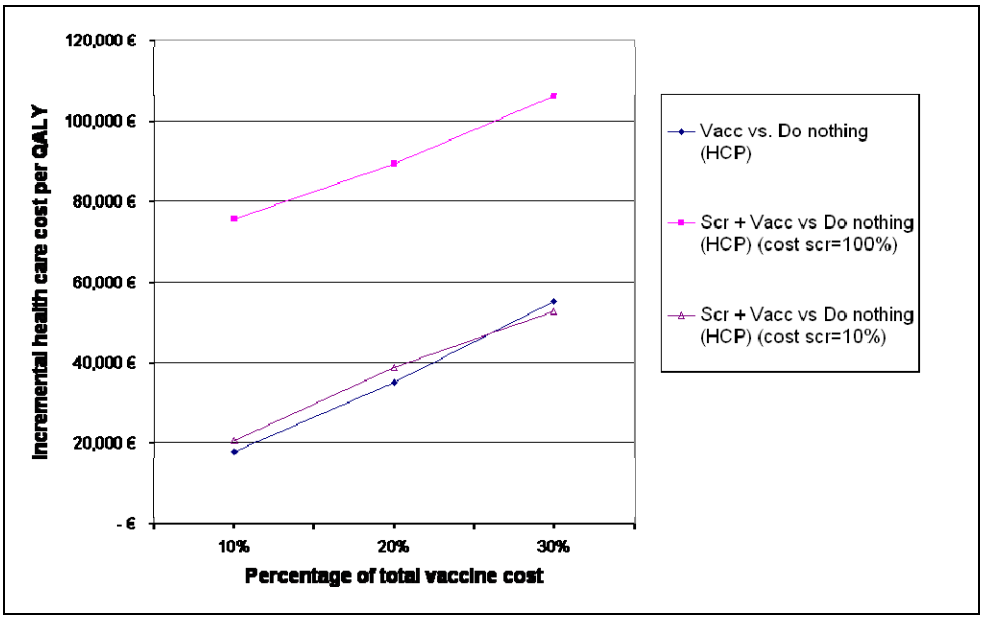


Figure 46 shows the relation between the cost-effectiveness and the vaccine and screening cost. The cost of the vaccine plus the personnel costs of health care workers needs to be lowered to 20% in order to make the intervention cost-effective. The scenario screening and vaccinating remains not cost-effective. Both strategies become comparable, i.e. both cost-effective at 20% of the vaccine cost, if the screentest can be done at only 10% of the initial cost.

Figure 47: ICER's in LY's for different percentages of price of vaccine and screentest

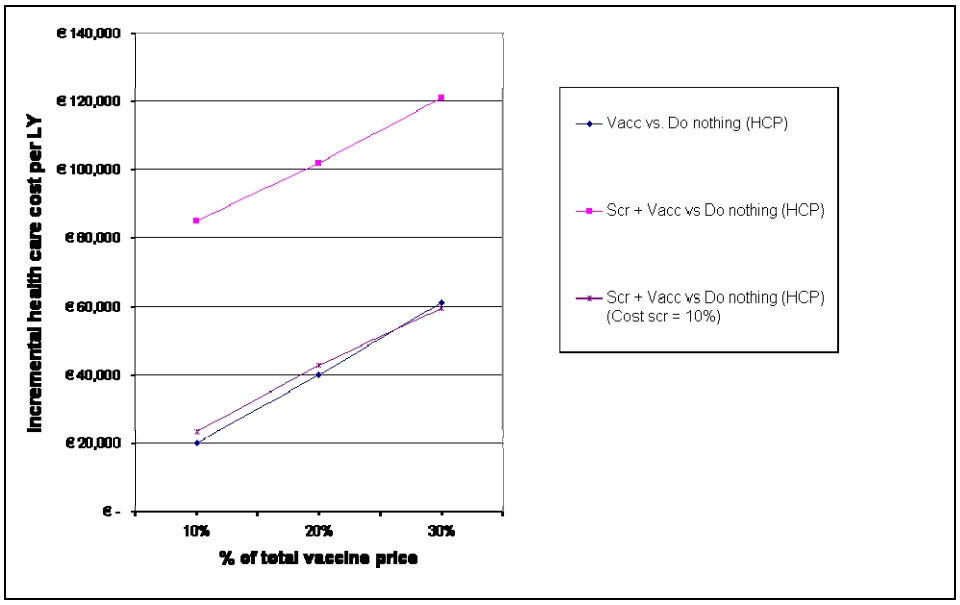


Figure 48: ICER's from the health care payer perspective for the strategy screen + vaccinate vs. do nothing for different levels of compliance to the screentest and different costs per test.

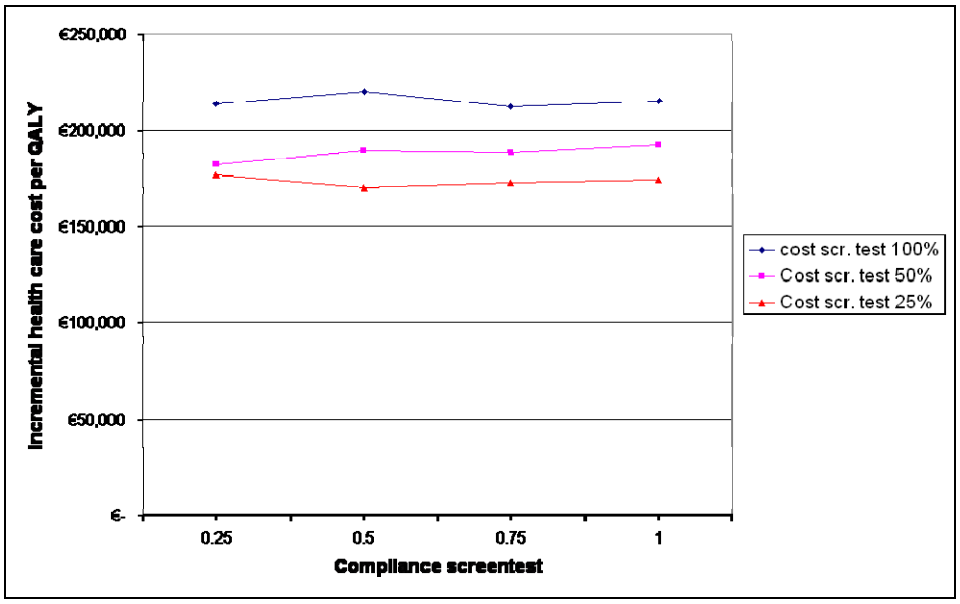


Figure 49: ICER's from the health care payer perspective for the strategy vaccinate vs. screen + vaccinate for different levels of compliance to the screen test and different costs per test.

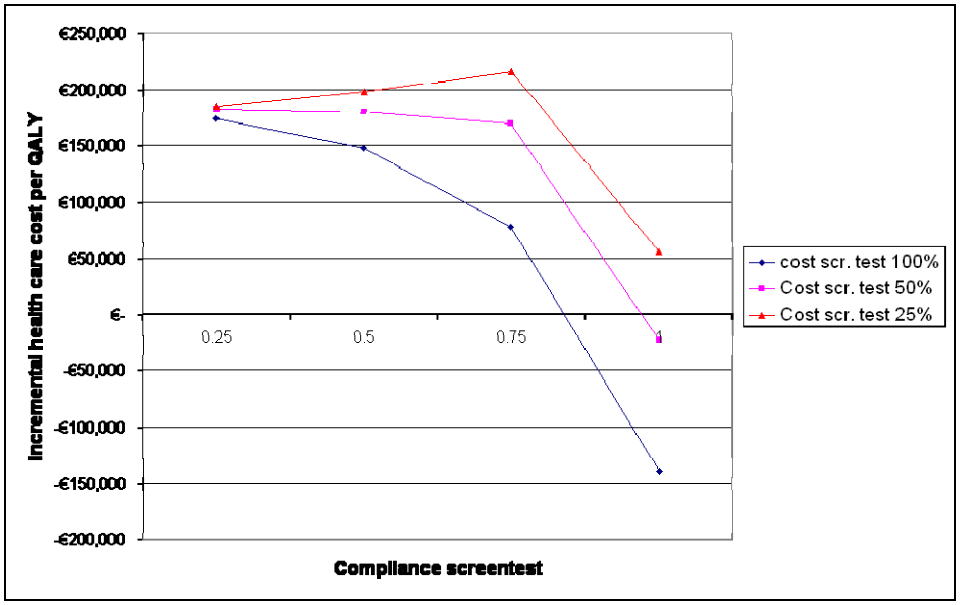


Figure 50: Incremental cost-effectiveness ratios for different scaling factors for quality of life scores for a hepatitis A episode.

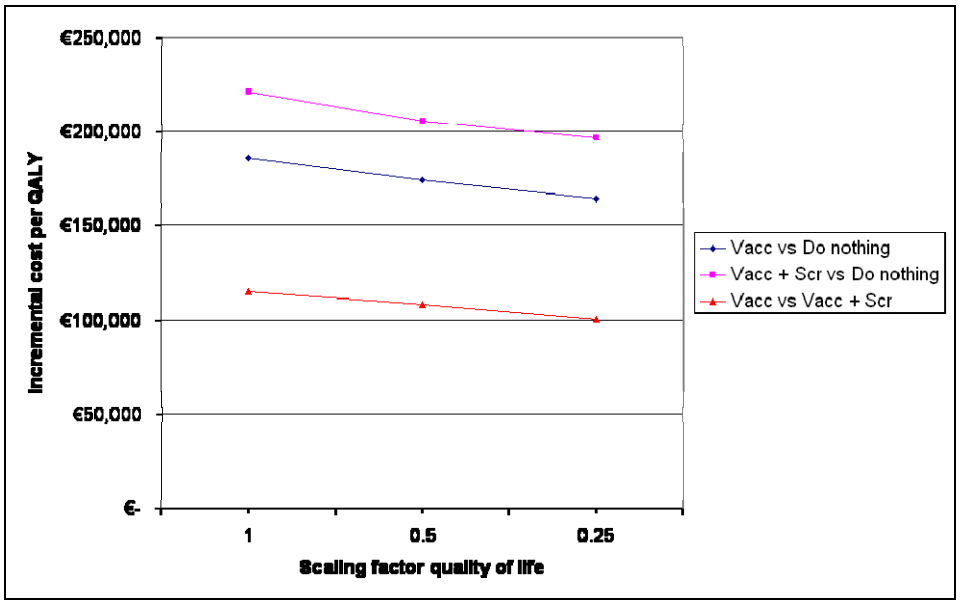


Figure 50 indicates that the ICER does not dramatically change as the quality of life score for a hepatitis A episode becomes lower. With a score of 50% and 25% of the value we obtained from the surveys the intervention still remains heavily cost-ineffective.

5 APPENDICES

APPENDIX A

SURVEYS DEVELOPED FOR REPORTED SYMPTOMATIC HEPATITIS A CASES

INSTRUCTIES ENQUETE HEPATITIS A

Er zijn **3 vragenlijsten**, elk zowel in het Nederlands als in het Frans

- Vragenlijst A / questionnaire A
- Vragenlijst B1 / questionnaire B1
- Vragenlijst B2 / questionnaire B2

En er zijn **2 begeleidende brieven**, elk zowel in het Nederlands als in het Frans:

- Brief A / lettre A
- Brief B/ lettre B

Instructies bij melding van een nieuw geval:

1) Achterhaal bij de melder (labo of arts), het adres, en zo mogelijk telefoonnummer en de geprefereerde taal (met als enige opties Nederlands of Frans) van de patient (of diens ouders voor minderjarigen)
2) Geef de patient een unieke code, bestaande uit de lettercode voor de provincie (van uw uitsturende dienst: A, L, OV, VB, WV) en volgnummer (iedere provincie begint vanaf nummer 1). Bijvoorbeeld de eerste patient uit Antwerpen krijgt code A001, de eerste patient uit Vlaams Brabant krijgt code VB001, de vijftiende patient uit West-Vlaanderen krijgt code WV015.
3) Voeg de nieuwe naam en code toe aan een administratieve tabel die u bewaart (zie bijgevoegde model)
4) Kies Nederlands of Frans, en schrijf op telkens 1 exemplaar van een blanco vragenlijst A, B1 en B2 rechts bovenaan elk blad de code van de patient.
5) Stel een **postpakket A** samen bestaande uit
   a. begeleidende **brief A**
   b. vragenlijst A (met code in rechtsbovenhoek)
   c. voorgefrankeerde enveloppe geaddresseerd aan **uzelf**
6) **Stuur postpakket A onmiddellijk** op naar de patient (maximum drie dagen na melding), zet versturingsdatum in administratieve tabel
7) Stel voor dezelfde patient een **postpakket B** samen bestaande uit
   a. begeleidende **brief B**
   b. vragenlijsten B1 en B2 (telkens met patientcode in rechtsbovenhoek)
   c. voorgefrankeerde enveloppe geaddresseerd aan **uzelf**

8) Na ontvangst van ingevulde vragenlijst A**, vul administratieve lijst aan met datum ontvangst**
9) Bij niet-ontvangst van een ingevulde vragenlijst A, **10 dagen** na versturing, contacteer de patient ter **herinnering** (preferentieel telefonisch)
10) **Stuur ca. drie weken** na de datum van melding **postpakket B** naar de patient (zet versturingsdatum in administratieve tabel), **onafgezien van ontvangst vragenlijst A**
11) Na ontvangst van ingevulde vragenlijsten B1 en B2**,** vul **administratieve lijst** aan met datum ontvangst
12) Bij niet-ontvangst van ingevulde vragenlijsten B1 en B2, ca. 10 dagen na versturing, contacteer de patient ter **herinnering** (preferentieel telefonisch)
13) **Copieer** ingevulde vragenlijsten A, B1 en B2 per patient en bewaar de copijen
14) **Stuur** de originele ingevulde vragenlijsten A, B1 en B2 per patient door naar (noteer datum versturing op administratieve lijst):

Jeroen Luyten
Centrum voor de Evaluatie van Vaccinatie
Epidemiologie en Sociale Geneeskunde
Universiteit Antwerpen
Campus Drie Eiken
Universiteitsplein 1
2610 Wilrijk

VRAGENLIJST B1

1. Welke van de volgende symptomen traden op ten gevolge van uw hepatitis infectie? Meerdere vakjes kunnen hier worden aangeduid.

- ☐ gele verkleuring van de huid
- ☐ gele verkleuring van de ogen
- ☐ algemeen moe en lusteloos
- ☐ misselijkheid
- ☐ donkere urine
- ☐ diarree
- ☐ bleke stoelgang
- ☐ verharding op de buik
- ☐ maag- of darmklachten
- ☐ pijn op de borst
- ☐ hoofdpijn
- ☐ andere, namelijk.....

2. Hoeveel dagen bent u ziek geweest ten gevolge van uw hepatitis A infectie?

……..... dagen

3. Hoelang bent u niet kunnen gaan werken omwille van uw hepatitis A infectie?

……... werkdagen (reken ook halve dagen mee)

4. Heeft er iemand u tijdens deze ziekteperiode extra bijgestaan (bijvoorbeeld met boodschappen doen, eten maken e.d.)?

☐ Neen → ga naar vraag 5

☐ Ja → Zo ja, verduidelijk:

Wie heeft u bijgestaan? (meerdere opties mogelijk)

- ☐ een familielid (bijvoorbeeld ouder, grootouder, kind, kleinkind, broer, zus)
- ☐ een vriend of kennis
- ☐ professionele hulp
- ☐ iemand anders: ……

Heeft u deze perso(o)n(en) betaald?

- ☐ Neen
- ☐ Ja , namelijk een totaalbedrag van ……. EURO

5. Is iemand anders dan uzelf niet kunnen gaan werken omwille van uw hepatitis A infectie?

☐ Neen → ga naar vraag 6
☐ Ja, namelijk in totaal …… werkdagen (Tel alle dagen van alle betrokken personen op, ook halve dagen)

6. Hoeveel keer heeft u de huisarts geraadpleegd voor uw hepatitis A infectie?

...…….keer waarvan …….. huisbezoeken

7. Hoeveel keer heeft u de specialist geraadpleegd voor uw hepatitis A infectie?

...…….keer

8. Heeft u geneesmiddelen (met of zonder voorschrift) moeten nemen ter behandeling van Hepatitis A?

□ Neen → ga verder naar vraag 9

□ Ja → Indien ja, vermeld op de stippellijnen waartegen u medicatie heeft genomen en indien mogelijk de naam van het medicament:

……
……
……
……
……
……
……..

9. Heeft men bloed genomen bij u omwille van Hepatitis A?

□ Neen
□ Ja , namelijk in totaal …….. keer

10. Is er een echografie gedaan omwille van Hepatitis A?

□ Neen
□ Ja, namelijk in totaal ……keer

11. Heeft men nog andere onderzoeken gedaan bij u (röntgenstralen, scanner,…) omwille van Hepatitis A?

□ Neen
□ Ja, namelijk ……
……

12. Heeft u een levertransplantatie ondergaan omwille van Hepatitis A?

□ Neen
□ Ja

13. Bent u naar de spoeddienst gegaan omwille van Hepatitis A?

□ Neen
□ Ja

14. Bent u gehospitaliseerd geweest omwille van Hepatitis A?

□ Neen
□ Ja
Indien ja, geef aan voor hoeveel nachten: ……nachten

15. Hoe of waar denkt u dat u hepatitis A heeft opgelopen? (Meerdere vakjes mogelijk)

□ In het buitenland
□ In een restaurant
□ Door contact met anderen
□ Andere ……

16. Bereidt u tijdens uw professionele bezigheden voedsel voor anderen? (kok, keukenhulp, beenhouwer,…)?

□ Ja
□ Neen

17. Bent u de laatste 2 maanden in het buitenland geweest?

□ Neen
□ Ja → Zo ja, welke landen?
……
……

18. Zijn er personen in uw omgeving (familie, vrienden, collega's,…) die hepatitis A hebben gehad kort <u>voordat</u> u besmet raakte?

□ Ja
□ Neen

19. Zijn er personen in uw omgeving (familie, vrienden, collega's,…) die hepatitis A hebben gehad kort <u>nadat</u> u besmet raakte?

□ Ja
□ Neen

20. Heeft men, omwille van uw hepatitis A infectie, bij familieleden of kennissen inentingen gegeven?

□ Neen
□ Ja → Zo ja, bij hoeveel mensen? ……

21. Was u voor uw infectie met hepatitis A al eens gevaccineerd geweest tegen hepatitis A (geelzucht)?

□ Neen
□ Ja

INDIEN U NOG BIJKOMENDE OPMERKINGEN HEEFT OVER UW ERVARING MET HEPATITIS A OF DEZE VRAGENLIJST, GELIEVE ZE DAN HIER TE GEVEN:

……
……
……
……
……
……
……
……
……
……
……

GELIEVE DE INGEVULDE VRAGENLIJSTEN B1 EN B2 ZO SNEL MOGELIJK IN BIJGEVOEGDE ENVELOPPE TERUG TE STUREN.
HARTELIJK DANK VOOR UW MEDEWERKING!

QUESTIONNAIRE B1

1. Quels symptômes avez-vous eu à cause de votre infection avec hépatite A? Vous pouvez cocher plusieurs cases.

- ☐ coloration jaune de la peau
- ☐ coloration jaune des yeux
- ☐ sans énergie ou volonté
- ☐ nausée
- ☐ urine obscure
- ☐ diarrhée
- ☐ selles pâles
- ☐ durcissement du ventre
- ☐ maux d'estomac ou des intestins
- ☐ douleur de poitrine
- ☐ maux de tête
- ☐ autre, c'est-à dire.....

2. Combien de jours avez-vous été malade pour cause d'hépatite A?

……..... jours

3. Combien de jours de travail avez-vous manqué pour cause d'hépatite A ?

……... jours ouvrables (précisez à la demi journée près)

4. Quelqu'un vous a-t-il assisté pendant votre période de maladie (par exemple pour faire des courses, cuisiner, etc.) ?

☐ Non → continuez avec question 5

☐ Oui → Si oui, clarifiez:

Qui vous a assisté ? (plusieurs choix possibles)

- ☐ une membre de la famille (par exemple un parent, grand-parent, enfant, petit-enfant, frère, soeur)
- ☐ un ami ou une connaissance
- ☐ un professionel
- ☐ quelqu'un d'autre: ……

Avez-vous payé cette personne/ces personnes?

- ☐ Non
- ☐ Oui, un montant total de ……. EURO

5. D'autres personnes ont-elles dû interrompre leur travail à cause de votre hépatite A?

☐ Non → continuez avec question 6

☐ Oui, au total …… jours ouvrables (Donnez le total pour toutes les personnes concernées, incluez aussi les demi journées).

6. Combien de fois avez-vous consulté le médecin de famille pour votre hépatite A?

..…….fois dont …….. visites à domicile

7. Combien de fois avez-vous consulté le spécialiste pour votre hépatite A?

...…….fois

8. Avez-vous dû suivre un traitement à base de médicaments (avec ou sans prescription) pour votre hépatite A ?

□ Non → continuez avec question 9

□ Oui → Si oui, mentionner ci-dessous l'action des médicaments pris et si possible aussi leur nom:

……
……
……
……
……

9. Avez-vous effectué des prises de sang pour votre hépatite A?

□ Non
□ Oui , au total …….. fois

10. Avez-vous passé des échographies pour votre hépatite A?

□ Non
□ Oui, au total ……fois

11. Avez-vous passé d'autres examens (rayons X, scanner, …) pour votre hépatite A?

□ Non
□ Oui, c'est-à-dire ……
……

12. Avez-vous subi une transplantation du foie pour votre hépatite A?

□ Non
□ Oui

13. Etes-vous allé aux urgences à cause de votre hépatite A?

□ Non
□ Oui

14. Avez-vous été hospitalisé pour votre hépatite A?

□ Non
□ Oui
Si oui, mentionnez combien de nuits: ……nuits

15. Comment pensez-vous avoir attrapé l'hépatite A? (plusieurs possibilités)

□ à l'étranger
□ dans un restaurant
□ par contact avec quelqu'un
□ autre: ……

16. Préparez-vous quotidiennement de la nourriture pour d'autres dans votre profession (cuisinier, boucher, ...) ?

□ Oui
□ Non

17. Êtes-vous allé à l'étranger ces deux derniers mois?

□ Non
□ Oui
Si oui, dans quels pays?
……
……

18. Des personnes dans votre environnement (famille, amis, collègues, …) ont-elles attrapé l'hépatite A peu de temps <u>avant</u> vous?

□ Oui
□ Non

19. Des personnes dans votre environnement (famille, amis, collègues, …) ont-elles attrapé l'hépatite A peu de temps <u>après</u> vous?

□ Oui
□ Non

20. Des membres de votre famille ou des amis ont-ils reçu des injections suite à votre infection par le virus de l'hépatite A?

□ Non
□ Oui
Si oui, combien de gens? ……

21. Avez-vous déjà été vacciné contre hépatite A (jaunisse) avant votre infection ?

□ Non
□ Oui

VEUILLEZ ECRIRE CI-DESSOUS VOS REMARQUES EVENTUELLES SUR VOTRE EXPERIENCE AVEC L'HEPATITE A OU SUR CE QUESTIONNAIRE:

.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....

MERCI BEAUCOUP POUR VOTRE PARTICIPATION!

APPENDIX B

ECONOMIC EVALUATIONS OF HEPATITIS A VACCINATION PROGRAM OPTIONS

1. Review of studies on the cost of an outbreak of Hepatitis A
    a. 1.1 A short analysis of different ways to estimate the cost of an outbreak of Hepatitis A.

To calculate the economic impact of an outbreak two separate datasets need to be estimated. The total cost of an outbreak is:

C(outbreak) = P.X

with X the total amount of resources used because of the outbreak and P the price of each resource. The total amount of resources used needs to be interpreted both direct and indirect. So data need to be found on the one hand on the amount and distribution of medical care consumed and economic value lost due to the outbreak, and on the other hand everything needs to be valued.

Ideally an outbreak is immediately documented by health authorities, both in resources used and prices paid. However, normally the cost of an outbreak is calculated retrospectively by first identifying cost categories, then consulting data or interviewing cases and estimating a value as proxy for the price.

If no data are available, costs can be estimated by a model that simulates an outbreak.

We briefly comment on the methods for estimating costs that were used in the retrieved articles.

1.1.1 Retrospectively collecting data from databases of official services involved.

This method is used in the following publications: Dalton et al.[84], Demicheli et al.[90], Lucioni et al.[91], Tolsma et al[80]. and Todd[78].

Direct costs were generally subdivided in GP-costs, specialist visits, diagnostic examinations, drugs, hospital costs, health department costs, outpatient care and other expenses. GP- costs and costs for drugs were estimated by using average physician fees and national price lists for all diagnostic and pharmaceutical items, according to the point of view that is taken. (In some countries where patients don't have to pay for health care this cost is zero from the individual, but not from a societal point of view.) Costs related to specialist visits were often estimated by using questionnaires for the amount and official price lists for the price. Health department costs were usually estimated by using diary and payroll records. The costs of evaluating suspected hepatitis A cases was estimated by calculating the number of hepatitis A serologic tests that were in excess (and attributable to the outbreak) compared to previous months. Costs of evaluating tests was based on average physician fees. The costs of immune globulin administration was often estimated by contacting hospitals for the number of injections and multiplying it with the market price. One study (Demicheli et al.[90]) also counted for miles travelled by car using an Italian Automobile Club price list.

Indirect costs were mainly business losses or productivity losses. These were harder to find in official databases and were often estimated by using questionnaires.

Costs of business losses from companies or restaurants involved, were for instance estimated by the decreased profits during the year of the outbreak compared to the profits of the previous year.

Productivity losses were calculated on the basis of the mean amount of time lost from performing routine productive duties by patients and relatives of patients valued by average national earnings (per hour) and imputed value of household work. If the patient was a salaried employee, the income lost was only included from the societal perspective. From the individual perspective indirect costs depend on the social insurance system. Lucioni et al[91]. also include school and university days lost as an indirect cost, also based on the hourly average national (or regional) income. For relatives the cost of lost free time was valued by using the hourly per capita regional GDP.

1.1.2 Cost-data collected afterwards by interviewing a sample of cases

One study (Sansom et al.[89]) was based on data provided by interviews of the patients. Investigators collected self-reported medical costs associated with hepatitis A and the estimated portion covered by health insurance, as well as lost workdays, wages, and the portion covered by sick leave. Based on the reported data per age-group, gender, hospitalization status, … medical costs obtained from the sample were imputed to the entire case-load.

A disadvantage of using sample data (questionnaires, interviews,…) might be that direct costs can be overestimated since the average cost of the sample is expanded to the entire population although marginal costs of extra patients may be smaller because of the existence of fixed costs. Indirect costs on the other hand are probably underestimated in all studies. It is nearly impossible to estimate accurately the impact of an outbreak on all economic activity (f.e. tourism).

1.1.3 Sending questionnaires to (a sample of) cases

Bownds [85] et al and Chossegros [93] et al used questionnaires to collect their main information.

Bownds et al. reached 145 persons from the entire list of 590 outbreak victims. Based on the responding surveys an estimation was made, adjusting for unemployment, including lost wages, extraordinary child care costs and health care utilization. The prices of the resources used were found in price lists of reporting systems. Multiplication yielded total expenditures on direct costs for the sample. Indirect costs were derived by using a subset of the respondents who provided complete employment information. Average income was calculated and expanded to the entire group. This may be misleading since such estimates do not include employer costs of lost productivity. Moreover there is possibly an information bias since there is no reason to believe that the group of respondents had the same characteristics as the ones who could not be reached.

The second study (Chossegros et al.) screened serum samples from non-hospital medical laboratories in the area to identify 100 patients with acute hepatitis A. A questionnaire was addressed to these 100 subjects 1 year later requesting information on health care expenditures and work loss related to their episode of infection. Incomplete answers were completed by telephone. These data were eventually combined in average costs for medical expenditures and for work loss per patient.

For both studies also the focus on average estimates may be misleading because of fixed costs.

1.1.4 Contacting GP's and interviewing them on their experience with HAV and correcting for the limited sample by a Delphi-technique.

Berge et al. [79] targeted geographic areas with high rates of hepatitis A infection and contacted general and family practitioners, gastroenterologists and infectious disease specialists. 42 of them responded to provide data on the treatment they had done during a 3-year period. This includes mainly direct medical treatment (and corresponding expenses) but if possible also the number of work days lost was noted.

For topics where the sample was insignificant (e.g. fulminant hepatitis) an expert panel was consulted to describe a typical treatment pattern and the corresponding cost (Delphi-method). Of all respondents median prices were used to estimate a typical

hepatitis A treatment pathway. If possible official medical price lists were used. The costs of work days lost were derived from age specific data on work-force participation and compensation.

1.1.5 Simulation models

If there is an absence of data suitable for the study of the economic impact of an outbreak of hepatitis A, simulation models can be constructed in order to make estimations. Meltzer et al [125]constructed two models, one for the perspective of a restaurant-owner and one for the societal perspective. Based on parameters to be found in official statistics with published estimates on hepatitis A the cost of the disease is calculated over the next 30 years. The costs are on the one hand health department costs and medical costs (direct costs) and on the other hand work-loss costs and restaurant losses associated with a public announcement (indirect costs).

This way of describing costs ultimately relies on what is known from previous outbreaks so it is not a real alternative for other methods. On the other hand it allows making estimates without depending too much on the chance of very specific events occurring.

The economic cost of a Hepatitis A outbreak

Methods

On April 28, 2008 we performed the following search in Pubmed, NHSEED, EconLit and DARE: (cost* OR economic) AND outbreak* AND "hepatitis A". The search in PUBMED resulted in 76 different publications. In web of science, NHSEED and DARE we respectively found 102, 11 and 0 articles. After elimination of duplicates and reading of all abstracts, 22 full-text articles were retrieved. The other articles were excluded because of their unique epidemiological content. Of the 22 articles considered, 7 included fairly comparable data on the cost of an outbreak, which are summarized in table 70. The relevant information related to outbreaks was extracted from 6 other articles in the text belowTPTP20PTPT. The nine articles left did not contain economic information.

Results

In this section we summarize the 14 articles considered relevant following our search described above.

Most estimates need to be interpreted conservatively because of difficulties in describing all costs generated by the outbreak. Both total costs and costs per case are presented. Total costs per case make it easier to compare between the different outbreaks bearing in mind the existence of fixed costs. Fixed costs will be allocated over a smaller number of cases in smaller outbreaks, and thus may show greater total costs per case compared to a larger outbreak in the same setting. For the smaller-type outbreaks, the marginal cost, i.e. the cost of an extra case, will be less than the calculated average. All outbreaks were documented in different ways. We attempted to impose a general framework on the cost calculations in order to be able to compare them better.

First, 7 outbreaks are summarized in general terms. Then, in the next section, we also present estimates for the cost-of-illness per case, unrelated to outbreaks, which were recovered from studies in the same country. In these estimates the cost of intervention and control is not, or not sufficiently, included, thus representing underestimations of the true economic impact of hepatitis A. All costs described in this article were brought to $US 2007. We used PPP's from the OECD health data 2007 to convert to $US.

To capture price effects we used for direct costs the CPI for medical care, for indirect costs the CPI for all items, both from the US Bureau of Labour Statistics. We chose for this approach, i.e. first converting and then inflating instead of the opposite, to avoid the effect of different inflation rates in the countries considered which would distort the comparability.

---

20 One also documented the cost of an outbreak, but was in Danish and is therefore not discussed extensively 126. Howitz, M.F., et al., [The economic impact of an epidemic of hepatitis A among men who have sex with men]. Ugeskr Laeger, 2007. 169(41): p. 3489-92..

3.1 Foodborne outbreaks

3.1.1 A food-borne outbreak of hepatitis A in Denver, Colorado, US in 1992 [84]

In 1992 an outbreak of hepatitis A associated with a catering facility, resulted in 43 cases and the potential exposure of 5,000 persons who attended parties catered by the food handler. Initially only 50 food handlers were given immune globulin prophylaxis. Later when the potential breadth of the outbreak became clear, more than 16,000 people received immune globulin prophylaxis.

The total cost of this outbreak was estimated at $1.38 million, or $32,290 per case. Eight percent were indirect costs, 92 % direct costs. Total direct costs were $29,809 per case of which $27,942 (94 %) were disease control costs and $1,867 (6 %) direct medical expenses for treatment. Most of the disease control costs were for immune globulin injections (65 %). This is an underestimation since immune globulin given by the approximately 1,400 private physicians was not included. Direct medical expenses were both for hospitalized and for non-hospitalized cases. However only 2 of 43 cases were hospitalized but made up 33% of the costs of illness for all cases. Total indirect costs were estimated at $2,480 per case. In this figure are included both business and productivity losses. Business losses ($1,502 per case) were due to lost profits as well as the food discarded by the catering company. Productivity losses due to these 43 cases, based on median duration of absence, average national earnings and imputed value of household work, were estimated at $978.

This outbreak demonstrates that the cost of an outbreak can be substantially higher than direct medical costs for cases. Outbreak control measures can be a major component of the total cost of an outbreak. The direct medical cost of illness was only 7 % of the outbreak control costs. Public notification can lead to an overconsumption of prophylaxis. Sixteen thousand people received IG while only 5,000 were potentially exposed. Compared with other outbreaks the total costs per detected case are much higher, probably because the outbreak was food-borne (at least initially) and not limited to person-to-person transmission.

An outbreak of hepatitis A in Puglia, Italy[91]

In 1996 a total of 5889 cases of hepatitis A were identified during an outbreak in Puglia, Italy. The primary cause of the outbreak was consumption of contaminated food, with a contributory factor of person-to-person transmission. Information of resources used was obtained by taking a random sample of 250 patients. 86% of the sample patients were aged between 11 and 30. Ninety percent of the cases was treated in hospital for 9.3 days as outpatient and for 15.3 days as inpatients (with nights spent at the hospital). Preventive procedures were recommendations to the public on handling and consuming raw seafood. No immunization program was implemented to control the outbreak which made that the outbreak did not wane for several months.

The total cost of this outbreak was $36,290,828. Direct costs were $28,398,494 or 78 % of total costs. Indirect costs were $7,892,334 or 21 % of total costs. This is relatively low in view of the high unemployment rate in the region, and the fact that losses to tourism were ignored. The lion share of all costs were costs of hospitalization, i.e. $23,987,169 or 66 % of total costs. This can be explained by the high hospitalization rate and the older age of the patients, indicating more severe symptoms. The costs per patient were $6,162. The total cost of the outbreak corresponded to 0.04 % of the regional GDP in 1996.

3.1.3 An outbreak in Toronto related to a food-handler [88]

In the article it is stated that foodborne outbreaks appear regularly in Canada and intervention programs are implemented timely. Approximately 3 incidents with infected food handlers occurred per year from 2001 to 2004.

Outbreak control measures in Canada were described as typically including communicable disease investigation, food-inspection and control, risk communication and immunization and surveillance of secondary cases. The median number of immunized individuals was 5,750 in incidents with large interventions.

In August 2002 an outbreak was identified in Toronto, related to a food handler in a high-volume grocery store, located in a high-density urban area. The eventual number of cases was 3, but the number of people given post exposure prophylaxis was remarkably high: 19,208 immunizations. The total public health cost corresponded to $601,440 or $200,480 per reported case. The cost-of-illness of this outbreak was not discussed but would be negligible compared to the outbreak control costs.

3.2 Outbreaks in schools

3.2.1 A small outbreak of hepatitis A in Narzole, Italy [90]

During the period December 1993 – March 1994 11 cases of Hepatitis A were reported, mainly children. The source of the outbreak is unknown but either related to a state school or a day care centre for children from broken homes. There also is a catering facility at the centre and some children eat their lunch there. Outbreak control measures were interviews of the cases, tracing of all family and school contacts and offering gammaglobulin prophylaxis to them. All cases were hospitalized

The total cost of this outbreak was estimated at $140,422, or $12,766 per case. Direct costs were 84 % of total costs, indirect costs 16 %. The direct costs totaled $118,499 in which only $1,622 (i.e. 1% of total costs) were outbreak control costs. The direct medical expenses for the 11 cases represented 83 % of all costs. Hospitalizations took up 75% of the total cost of the outbreak. However a large part of hospitalization costs were fixed, and would decrease proportionate to rising caseload. Indirect costs included only productivity losses and amounted to $21,923. This share in total costs is rather small since the epidemic involved mainly children. Most productivity losses were incurred through parental work time spent caring for children.

The cost structure of this outbreak might be atypical because of some special characteristics. The outbreak was rather small with considerable fixed costs leading to a relatively greater fraction of direct costs, compared to larger outbreaks. Moreover most of these cases were children which may imply relatively lower indirect costs compared to adults. If the outbreak had expanded then indirect costs would be the major component of (marginal) costs.

3.2.2 A school outbreak in Liverpool [92]

In January 2006, nine symptomatic hepatitis A cases occurred in a socio-economically deprived area of Liverpool with high levels of drug abuse. The main route of transmission was from person to person, and five cases were linked within a primary school. Since previous outbreaks in the area around Liverpool caused up to 300 cases, a range of outbreak control measures were taken. Post exposure vaccination was considered a viable strategy and was offered to all of the school children and staff, with a total of 100 saliva tests taken and 188 vaccines administered.

This study had its focus on the cost-effectiveness of the intervention. Total costs including direct medical expenses and indirect costs of the outbreak were not discussed. The outbreak control measures made up a total expense of $7,818, or $869 per infected case.

3.3 Outbreaks among adults

3.3.1 An outbreak in a mid-sized urban community, Spokane, Washington, US [85]

An outbreak of hepatitis A occurred during 1997 and 1998 in Spokane, resulting in 590 cases of acute hepatitis A. Four hundred of them occurred in 1998. The outbreak was thought to be associated with increased IV methamphetamine use. Approximately 6 % was hospitalized for an average of seven days. A total of 7,134 individuals received immune globulin in public health departments. Costs were derived from a sample of 145 respondents. The ones unreachable may have had a lower socio-economic status since the outbreak was associated with increased drug use. This implies that the indirect costs may have been overstated. The authors state that direct medical expenditures are probably underestimated since the symptoms may have been more serious, due to poor health access.

The total cost of this outbreak was estimated at $3,271,537 with 35 % direct medical costs, 42 % outbreak control costs and 22 % indirect costs. This is a low estimate since several cost-categories are kept out of the analysis. The outbreak control costs substantially exceed all other cost categories, indicating that the major costs to society are not always to be found with the case-patients. A total of no less than $1,389,978 was spent on administration of IG prophylaxis. Inpatient hospital care of 6 % of the cases is the largest fraction of direct medical costs of all cases combined. Indirect costs include lost salaries, but also child care costs. Average total cost per case is $5,545 with an average of $1,946 for medical care, $2,356 for handling IG to contacts and $1,243 costs of time losses. An outbreak like this can have an enormous impact on economic activity in a rural area.

3.3.2 An outbreak affecting homosexual men in Franklin County, Ohio, US [89]

Between November 1998 and May 1999 a total of 136 cases of hepatitis A were reported in the city of Colombus (Ohio), an increase of 325 % compared to the previous years. Of these cases, 118 (87%) were male adults and 47 (64%) identified themselves as 'men who have sex with men'. About 1 in 6 (18 %) of reported cases was hospitalized and 1 person died. Outbreak control measures consisted of community outreach, public notification and administration of immunoglobulin to 485 individuals who may have been exposed to hepatitis A.

The estimated total cost of the outbreak was $520,039 including approximately $220,615

(43 %) medical costs, $50,105 (10 %) outbreak control costs and $249,318 (47 %) indirect costs of lost productivity. The largest direct cost item was the cost of hospitalization, which constituted for 52 % of total direct costs and 27 % of total costs, despite the fact that it affected only a minority of patients. The costs per case were on average $3,824, with $1,991 direct and $1,833 indirect costs. Outbreak control costs were probably underestimated since no private IG provision was included. Additionally, 1 patient died and no attempt was made to estimate the associated costs of death and life-years lost.

3.4 Other estimates for the cost of an outbreak

Several other studies also documented the costs of outbreaks [Bauch et al [87], Postma et al [122], Chodick et al [127], Egoz [128], Patnaik et al [129], Howitz et al] [126], but the partial or implicit way of reporting does not allow to summarise these studies in the same manner as the outbreaks listed in the previous sections (3.1-3.7). All costs are in $US 2007.

Bauch et al. made a cost-utility analysis in which they incorporated public health interventions by attributing $430 per symptomatic case. Postma et al calculated an average cost of an outbreak of $9,545 based on registered outbreaks in Amsterdam.

Intervention costs contributed the most to direct costs (23% of total costs), with 100 doses of immunoglobulin administered per outbreak. Additional cost items were indirect costs (61%), hospital care (14%) and GP-visit and serology (2%). Chodick et al estimated the cost of preventive prophylaxis in an outbreak at $130 per case.

Egoz [128] described the cost of avoiding an outbreak of HAV through contaminated drinking water in 1985. In total 12,644 doses of immuneglobulin were administered to children and pregnant women, corresponding to a cost of $58,121. Patnaik et al reported on the outbreak control measures of an infected food worker in Colorado. IgG was administered to 693 individuals, corresponding to a cost of $54,678. Howitz et al reported on an outbreak causing 220 symptomatic cases in homosexuals, which costed $823,081 or 3,798$ per case.

Table 69: Total economic costs of an outbreak, specified according to different cost categories (costs per case, % of total costs) (in $2007)

Location	Denver, US	Spokane, US	Franklin County, US	Narzole, Italy	Puglia, Italy	Liverpool, UK	Toronto, CND
Main source of outbreak	Infected Food handler	Increased drug use	Homosexual men	School or daycarecentre for	Infected Food and pers. to pers.	Primary school	Infected Food handler
Nr of cases	43	590	136	11	5889	9	3
Direct costs	$1,281,800 ($29,809 ; 92%)	$2,538,004 ($4,301 ; 78%)	$270,720 ($1,991 ; 52%)	$118,499 ($10,773 ; 84%)	$28,398,494 ($4,822 ; 78%)	NS	NS
Direct treatment costs	$80,292 ($1,867 ; 6%)	$1,148,025 ($1,946 ; 35%)	$220,615 ($1,622 ; 42%)	$116,876 ($10,652 ; 83%)	$28,398,494 ($4,822 ; 78%)	NS	NS
Non-hospital costs	$54,195 ($1,260 ; 4%)	$445,760 ($756 ; 14%	$78,410 ($577 ; 15%)	$11,853 ($1,078 ; 8%)	$4,411,325 ($749 ; 12%)	NS	NS
Hospital costs	$26,097 ($607; 2%)	$702,265 ($1,190 ; 21%)	$140,527 ($1,033 ; 27%)	$105,024 ($9,548 ; 75%)	$23,987,169 ($4,073 ; 66%)	NS	NS
Direct control costs	$1,201,508 ($27,942 ; 87%)	$1,389,978 ($2,356 ; 42%)	$50,105 ($368 ; 10%)	$1,622 ($147 ; 1%)	NA	$7,818 ($869)	$601,440 ($200,480)
Prophylaxis used	IG	IG	IG	IG	NO	Vaccine	Vaccine & IG
Tests	$232,205 ($5,400 ; 17%)	NS	$381 ($3 ; 0%)	NS	NA	NS	NS
Prophylaxis costs	$785,064 ($18,257 ; 57%)	$1,389,978 ($2,356 ; 42%)	$22,290 ($164 ; 4%)	$318 ($29 ; 0%)	NA	$5,478 ($609)	$342,019 ($114,006)
Health personnel costs	$184,239 ($4,285 ; 13%)	NS	$27,434 ($202 ; 5%)	$1,304 ($119 ; 1%)	NA	$1,302 ($145)	$259,421 ($86,474)
other	NS	NS	NS	NS	NA	$1,036 ($115)	NS
Indirect costs	$106,653 ($2,480 ; 8%)	$733,533 ($1,243 ; 22%)	$249,318 ($1,833 ; 48%)	$21,923 ($1,993 ; 16%)	$7,892,334 ($1,340 ; 22%)	NS	NS
productive time lost	$42,083 ($979 ; 3%)	$733,533 ($1,243 ; 22%)	$249,318 ($1,833 ; 48%)	$21,923 ($1,993 ; 16%)	$7,180,231 ($1,219 ; 20%)	NS	NS
Other time lost	$64,570 ($1,502 ; 5%)	NS	NS	NS	$712,102 ($121 ; 2%)	NS	NS
Average Number of workdays lost	12.5TPT[21]TPT	9.1	12	7.5	12.8	NS	NS
Total cost	$1,388,452 ($32,290; 100%)	$3,271,537 ($5,545 ; 100%)	$520,039 ($3,824 ; 100%)	$140,422 ($12,766 ; 100%)	$36,290,828 ($6,162 ; 100%)	NS	NS

NS: Not stated, NA: Not applicable

[21] Median duration of absence of work

Table 70: Cost-estimates for hepatitis A patients in miscellaneous studies on the cost of illness (in $US2007)

First author	Tolsma et al [80]	Chossegros et al[93]	Berge et al [79]	De Juanes et al [94]	Todd [78]	Diel et al [95]
Region/year	US	France	US	Spain	US	Germany
Direct costs per case	$583	$655	$2.586	NS	NS	$1.020
Indirect costs per case	$967	$1.988	$7.361	NS	NS	$4315 / $449([22])
Total cost	$1.550	$2.782	$9.948	$764	$9.691	$5336 / $292

Table 71: Cost-estimates from CEA's for hepatitis A in the US, Canada and France (in $US 2007)

Author	Bauch et al. [87]	Jacobs et al.[96]	Myers et al.[97]	Péchevis et al.[98]	Jacobs et al. [96]	O'connor et al [83]	Smith et al [99]
Population studied	Universal Canada	Adolescents US	Chronic HCV US	Sec. infect. France	Children US	Adults US	Students US
Outbreak control costs	$430	NS	No	NS	NS	NS	NS
Direct costs per case	From $1000 to $1686	$985	$3783 (moderate case)	$356 (mild) $3355 (hosp.)	$668 (nonhosp) $9506 (hosp)	$183 (nonhosp.) $9219 (hosp.)	NS
Cost per case	From $1607 to $3189	$2658	NS	NS	NS	NS	$10491

22 For an adult/for a child

In conclusion, the economic impact of an outbreak with hepatitis A can be very high. In the five outbreaks described here, local economies had to face a cost ranging from $140,000 to $36 million in a short time span. The estimates on cost of illness in the outbreak studies seem to be higher than estimates based on calculations of the cost to individual cases. Post exposure prophylaxis is a major cost factor, especially for food borne outbreaks. Cost-effectiveness analyses often ignore these costs. If the epidemiological situation for which these CEA's are designed, makes it unlikely for an outbreak to occur, or if it is likely that outbreaks remain very small (and non-food borne), then the exclusion of outbreak-specific costs seems defensible.

Table 72: Comparison of direct costs for Cost-of-Illness Studies, Cost-effectiveness analysis and cost of outbreak studies for US adults

United States Direct costs per case for adults and adolescents (in $US 2007)			
cost-of-illness studies	Hadler (1991)	Berge et al (2000)	
Average direct cost per case	$1267	$2152	
% of hospitalizations	15%	14%	
cost-effectiveness analyses	Jacobs et al (2000)	O'connor et al (1999)	
Average direct cost per case	$985	$1,628	
% of hospitalizations	>10%	16%	
Cost-of-an-outbreak studies	Denver (1992)	Spokane (1998)	Franklin (1999)
Average direct cost per case	$29,809	$4,302	$1,991
% of hospitalizations	4%	1%	11%

2. Review of Cost-Effectiveness and Cost-Utility analyses on Hepatitis A vaccination

Table 73: Study Characteristics of cost-effectiveness and cost-utility analyses[23]

	Total Number of studies(n = 36)	
Study characteristics	**n**	**%**
Year of publication		
1990-1995	4	11
1996-2000	10	27
2001-2007	22	61
Population		
Infants	11	36
Children/pre/adolescent/	9	25
Adults/general Population	6	13
Health care workers	5	11
Travelers	3	6
Patients with chronic HCV	3	6
Military♣	3	6
Other high risk*	3	6
Vaccination Strategy		
Universal	18	36
Targeted	18	36
Other	13	26
Study Funding		
Industry	16	44
Non-industry	6	16
Not Reported	14	38
Region		
US	14	40
Canada	3	8
Europe†	13	37
Other	6	14

23 Notes: A study could assess more than one population and strategy therefore the percentages in these categories do not add to 100%; * College students, prison inmates, food service workers, patients attending STD clinic, personal contacts of HA case; † one study was included here but not for Tables 2-3, ♣ one study was included here but not for Tables 2-3 .

Table 74: Summary of Cost-effectiveness of Hepatitis A Vaccine, by Vaccination Strategies, Population and Intervention[24]

	Cost per LY or QALY					Cost per case prevented		
Study characteristics	**Total No. Studies**	**Total No. Comparisons**	**<$20,000 n(%)**	**$20,000-$100,000 n(%)**	**>$100,000 n(%)**	**Total No. Studies**	**Total No. Comparisons**	**Median**
Vaccination Strategy								
Universal	13	62	34 (55)	13 (21)	14 (23)	6	13	$5,335
Infant	7	36	24 (67)	8 (22)	4 (11) *	3	4	$390
Children/pre/adolescent	5	22	11 (50)	5 (23)	6 (27) †	3	7	$5,335
Adults	2	4	0 (0)	0 (0)	4 (100)	1	2	$297,485
Targeted	8	21	9 (43)	4 (19)	8 (38)	9	23	$18,258
Travelers						3	6	$26,046
Health care workers	3	9	1 (11)	2 (22)	6 (67)	2	3	$129,757
Military						2	6	$16,332
Other high risk***	5	12	8 (67)	2 (17)	2 (17)	3	8	$2,303
Other**	6	18	2 (11)	9 (50)	7 (39)	7	17	$19,033
Travelers						3	4	$23,555
Health care workers	2	8	0 (0)	4 (50)	4 (50)	2	3	$133,591
Patients with chronic HCV	2	8	1 (13)	5 (63)	2 (25)	1	1	$479,024
Adults/General population	1	1	0 (0)	0 (0)	1 (100)	2	6	$5,227

24 Notes: one study is not included in this table due to extremely poor quality and inability to understand the data related to the ICERs. One study reported ICER as disability-adjusted life year (DALY), one in $/patient immune (Jakiche 2007 [90])and one study reported ICER as death averted and these are not included here. One study (Rein et al. 2007117. Rein, D.B., et al., Cost-effectiveness of routine childhood vaccination for hepatitis A in the United States. Pediatrics, 2007. 119(1): p. e12-21.) did not have similar ICERs for cost per LY and cost per QALY for same comparisons, and therefore only QALY is reported in this table. *all ICERs from one study Rein et al. 2007,† all ICERs from one study (Bauch et al.2006), **This is a strategy of screening for HA antibodies and vaccinating susceptibles, ,*** other high risk: college students, infants, prison inmates, food service workers, patients attending STD clinic, personal contacts of HA case , Φ "other" :military and children, ΦΦall were from Krahn et al. 2003 unpublished[23], service workers, and household or school contacts of HA cases.

Other groupsΦ	1	1	1 (100)	0 (0)	0 (0)	1	2	$6,672
Population								
Infants	7	37	25 (57)	8 (22)	4 (11) *	3	4	$390
Children/pre/adolescent	5	22	11 (50)	5 (23) ΦΦ	6 (27) †	3	9	$5,832
Travelers						3	10	$25,836
Health care workers	3	17	1 (6)	6 (35)	10 (59)	2	6	$131,674
Adults/General population	3	7	2 (29)	0 (0)	5 (71)	3	12	$6,653
Patients with chronic HCV	2	10	1 (10)	5 (50)	4 (40)	1	1	$479,024
Military (all case prevented)						2	7	$11,474
Other high risk***	3	7	5 (71)	2 (29)	0 (0)	1	5	$0
Intervention								
HA vaccine	15	81	31 (38)	20(25)	28(35)	12	37	$10,271
HA/HB vaccine	10	17	9(53)	6(35)	0(0)	1	2	$0
Immunoglobulin						6	15	$26,979

Table 75: Summary of Cost-effectiveness of Hepatitis A Vaccine, by Study Characteristic and Methodological Factors

	Cost per Life year of QALY					Cost per case prevented		
Study characteristics	**Total No. Studies**	**Total No. Compari-sons**	**<$20,000 n(%)**	**$20,000-$100,000 n(%)**	**>$100,000 n(%)**	**Total No. Studies**	**Total No. Comparisons**	**Median**
Year of publication								
1990-1995						4	16	$25,836
1996-2000	5	14	7	2	5	5	28	$6,456
2001-2007	17	86	38	24	24	4	10	$390
Location								
US	13	48	21	14	13	1	2	$390
Canada	3	20	6	6	8			
Europe	1	1	1	0	0	11	51	$13,344
Other	5	31	16	7	8	1	1	$479,024
Funding								
Industry	13	55	34	11	10	3	12	$9,594
Non-industry	4	19	2	8	8	1	14	$5,584
Not reported	5	26	7	8	11	9	28	$26,769
Model Type								
Cohort	19	86	40	25	21	10	46	$9,595
Dynamic	3	13	4	2	8	1	2	$91,889
NR						2	6	$16,330
Work Loss Cost*								
Yes	17	51	29	11	11	7	19	$19,033
No	14	49	15	16	18	5	27	$5,335
Public Health Cost								
Yes	8	45	19	12	14	3	7	$19,033
No	13	55	25	15	15	10	47	$11,474

Table 76: Table of studies on the evaluation of vaccination

REF ID	Author	Population	Vaccine	Time Horizon (y)	Annual incidence (per 100,000)	Long-term vaccine efficacy	$/DOSE	Discount rate	Perspective	Outcome	ICER
UNIVERSAL											
INFANTS											
Universal vs. No Vaccination											
[96]	Jacobs	infants, all states, U.S.	HA	lifetime	low	20,40,60 y: 62%, 40%, 25%	$16	3%	societal	QALY	$15,843
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	QALY	$133,000
[96]	Jacobs	infants, U.S.	HA	lifetime	<50% national average	20,40, 60 y: 62%,40%, 25%	$16	3%	societal	QALY	$71,294
[130]	Das	infants, developed countries	HA	lifetime	10	12% ann. decline vaccine-induced anti-body	$45	3%	societal	QALY	$9,677
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	LY	$933,000
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7 - 22.6 (all of U.S.)	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	QALY	$28,000
[96]	Jacobs	infants, U.S.	HA	lifetime	50%-100% national average	20,40, 60 y: 62%,40%, 25%	$16	3%	societal	QALY	$15,617
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7 - 22.6 (all of U.S.)	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	LY	$199,000
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7 - 22.6 (all of U.S.)	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	CP	$284
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	14.1-22.6	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	QALY	<$O
[96]	Jacobs	infants, U.S.	HA	lifetime	100-199% national average	20,40, 60 y: 62%,40%, 25%	$16	3%	societal	QALY	<$O
[96]	Jacobs	infants, U.S.	HA	lifetime	>200% national average	20,40, 60 y: 62%,40%, 25%	$16	3%	societal	QALY	<$O
[115]	Valenzuela	infants (18+24 m), Chile	HA	50	(Age 1-50): 99, 260, 154, 56,31, 15,7,6	8, 28,48 y: 97%, 86%, 78%	$11	3%	societal	QALY	<$O
[115]	Valenzuela	infants (18+24 m), Chile	HA	50	(Age 1-50): 99, 260, 154, 56,31, 15,7,6	8, 28,48 y: 97%, 86%, 78%	$11	3%	societal	QALY	<$O
[115]	Valenzuela	infants (18+24, 18+54 m), Chile	HA	50	(Age 1-50): 99, 260, 154, 56,31, 15,7,6	8, 28,48 y: 97%, 86%, 78%	$11	3%	societal	QALY	$18,845
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	14.1-22.6	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	LY	<$O
[115]	Valenzuela	infants (18+24, 18+54) in Chile	HA	50	(Age 1-50): 99, 260, 154, 56, 31, 15,7,6	8, 28, 48 y: 97%, 86%, 78%	$11	3%	societal	LY	$30,838
[115]	Valenzuela	infants (18+24 m), Chile	HA	50	(Age 1-50): 99, 260, 154, 56, 31, 15,7,6	8, 28, 48 y: 97%, 86%, 78%	$11	3%	societal	LY	<$O
[115]	Valenzuela	infants (18+54 m), Chile	HA	50	(Age 1-50): 99, 260, 154, 56, 31, 15,7,6	8, 28, 48 y: 97%, 86%, 78%	$11	3%	societal	LY	<$O
[131]	Szucs	Age 1-15, Gernany	HA	30	NR	10y	NR	5%	societal	CP	<$O
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	HS	QALY	$143,000
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7 - 22.6 (all of U.S.)	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	HS	QALY	$40,000
[96]	Jacobs	infants, all states	HA	lifetime	14.1-22.6	20,40,60 y: 62%, 40%,25%	$16	3%	HS	QALY	$10,298
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	(Age 1-50): 99, 260, 154, 56, 31, 15,7,6	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	HS	QALY	$8,000

[115]	Valenzuela	infants (18+24 m), Chile	HA	50	(Age 1-50): 99, 260, 154, 56, 31, 15,7,6	8, 28,48 y: 97%, 86%, 78%	$11	3%	HS	QALY	$524
[115]	Valenzuela	infants (18+54 m), Chile	HA	50	(Age 1-50): 99, 260, 154, 56, 31, 15,7,6	8, 28, 48 y: 97%, 86%, 78%	$11	3%	HS	QALY	$293
[115]	Valenzuela	infants (18+24 m), Chile	HA	50	(Age 1-50): 99, 260, 154, 56,	8, 28,48 y: 97%, 86%, 78%	$11	3%	HS	LY	$919
[115]	Valenzuela	infants (18+54 m), Chile	HA	50	31, 15,7,6	8, 28, 48 y: 97%, 86%, 78%	$11	3%	HS	LY	$479
[119]	Lopez	Infants (12+18m) Argentina	HA	100 years	Case fatality rates: <14, 15-29,30-39,40-49,…,>80y: 140,180,210,360,810,1490,2630,3850	Annual rate of waning of sero-protection: 0.58%	$7	3%	Societal	Costs saved/ LY gained	$3429
[116]	Armstrong	Infants 1 y, US	HA	95 years	regionspecific, a decline of 1,4% per year,	annual 1,4%	NR	3%	societal	QALY	$1000
[132]	Ellis	Infants 1 y, Argentina	HA	50 years	7,3 - 678,3	NR	$8,50	3%	societal	QALY	<$0
[132]	Ellis	Infants 1+1,5 y Argentina	HA	50 years	7,3 - 678,3	NR	$8,50	3%	societal	QALY	$173-$2772
Universal vs. Targeted											
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	QALY	$132,000
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	LY	$927,000
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7 - 22.6 (all of U.S.)	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	QALY	$45,000
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7 - 22.6 (all of U.S.)	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	LY	$338,000
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7 - 22.6 (all of U.S.)	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	CP	$496
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	14.1-22.6	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	QALY	<$O
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	14.1-22.6	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	societal	LY	<$O
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	US	QALY	$143,000
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	6.7 - 22.6 (all of U.S.)	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	US	QALY	$57,000
[117]	Rein	infants, age 1-2 y, U.S.	HA	lifetime	14.1-22.6	20% ann. decline in antibody concentration (1-5 y), 5% (5+y)	$18	3%	US	QALY	$9,000
Universal vs.Other											
[130]	Das	infants, developed countries	HA	lifetime	10	12% ann. decline of vaccine-Induced antibody	$45-		societal	QALY	$16,551
[95]	Diel	infants + travelers, Gemany	HA/HB	30	NR	NR	$58-$67	5%	societal	CP	$71,532
[115]	Valenzuela	Infants (18+24, 18+54m) Chile	HA	50	(Age 1-50):99,260,154,56,31,15,7,6	8,28,48y:97%,86%,78%	$11	3%	HS	LY	$33,352
[115]	Valenzuela	Infants (18+24, 18+54m) Chile	HA	50	(Age 1-50):99,260,154,56,31,15,7,6	8,28,48y:97%,86%,78%	$11	3%	HS	QALY	$20,385
CHILDREN/PRE/ADOLESCENTS											
Universal vs. no vaccination											
[132]	Ellis	Age 1+6 Argentina	HA	50 years	7,3 - 678,3	NR	$8,50	3%	societal	QALY	$4829
[133]	Navas	Age 12, Spain	HA/HB	25	(Age 12-37): 15	25y:97%	$3	5%	Societal	LY	<$0
[133]	Navas	Age 12, Spain	HA/HB	25	(Age 12-37): 15	25y:97%	$3	5%	societal	DALY	<$0
[134]	Krahn	Age 10, Canada	HA/HB	Lifetime	(Age 0-60): 320, 71, 44, 42,40,47,37,20,11	10,30,50 y: 95%,81%,74%	$35	3%	societal	LY	$20,151
[134]	Krahn	Age 10, Canada	HA/HB	Lifetime	(Age 0-60): 320, 71, 44, 42,40,47,37,20,11	10,30,50 y: 95%,81%,74%	$35	3%	societal	LY	$21,511
[82]	Jacobs	Age 15, US	HA	NR	(Age 15-80): 109, 15 1, 111,55, 42,18, 18,18	10, 30, 70 y: 95%, 81%, 68%	$20	3%	societal	LY	<$0
[135]	Arnal	Age 13/14	HA	10	100-200	10 y: 90%	$21-$31	6%	Societal	CP	$5,335
[134]	Krahn	Age 10, Canada	HA/HB	lifetime	(Age 0-60): 320, 71, 44, 42,40,47,37,20,11	10 y: 90%	$35	3%	HS	QALY	$30,226

[134]	Krahn	Age 10, Canada	HA/HB	lifetime	(Age 0-60): 320, 71, 44, 42,40,47,37,20,11	10,30,50 y: 95%,81%,74%	$35	3%	HS	LY	$34,876
[[82]	Jacobs	Age 15, U.S.	HA	NR	(Age 15-80): 109, 15 1, 111,55, 42,18, 18,18	10, 30, 70 y: 95%, 81%, 68%	$20	3%	HS	LY	$18,904
[131]	Szucs	Age 11-15, Germany	HA/HB	30	NR	10y	NR	5%	TPP	CP	<$O
[131]	Szucs	Age 1-15, Germany	HA/HB	30	NR	10y	NR	5%	TPP	CP	<$O
Universal vs. Targeted											
[87]	Bauch	Age 9, Canada	HA/HB	lifetime	3.7	Ann. decline 1.7%-3.2%	$7	5%	Societal	QALY	<$O
[87]	Bauch	Age 15, Canada	HA	lifetime	3.7	Ann. decline 1.7%-3.2%	$8	5%	Societal	QALY	<$O
[87]	Bauch	Age 4, Canada	HA	lifetime	3.7	Ann. decline 1.7%-3.2%	$8-$28	5%	Societal	QALY	$583,200
[87]	Bauch	Age 4 + 9, Canada	HA	lifetime	3.7	Ann. decline 1.7%-3.2%	$8-$28	5%	Societal	QALY	<$O
[87]	Bauch	Age 4 + 15, Canada	HA	lifetime	3.7	Ann. decline 1.7%-3.2%	$8-$28	5%	Societal	QALY	$35,200
[87]	Bauch	Age 9, Canada	HA/HB	lifetime	3.7	Ann. decline 1.7%-3.2%	$7	5%	HS	QALY	<$O
[87]	Bauch	Age 15, Canada	HA	lifetime	3.7	Ann. decline 1.7%-3.2%	$8	5%	HS	QALY	$1,068,000
[87]	Bauch	Age 4, Canada	HA	lifetime	3.7	Ann. decline 1.7%-3.2%	$8-$28	5%	HS	QALY	$709,600
[87]	Bauch	Age 4 + 9, Canada	HA	lifetime	3.7	Ann. decline 1.7%-3.2%	$8-$28	5%	HS	QALY	$140,000
[87]	Bauch	Age 4 + 15, Canada	HA	lifetime	3.7	Ann. decline 1.7%-3.2%	$8-$28	5%	HS	QALY	$284,000
[136]	Bauch	Age 4+9 Canada	HA/HAHB	80 years	3,9	97%	$10-34	3%	HS	QALY	175,000
[136]	Bauch	Age 4+9 Canada	HA/HAHB	80 years	3,9	97%	$10-34	3%	societal	QALY	-77,000
[136]	Bauch	Age 9+9 Canada	HA/HAHB	80 years	3,9	97%	$10-34	3%	HS	QALY	-46,000
[136]	Bauch	Age 9+9 Canada	HA/HAHB	80 years	3,9	97%	$10-34	3%	societal	QALY	-835,000
[95]	Diel	Age lt- 15 + travelers,Gemany	HA/HB	30	(Age 1-65):2,9,9,6,6,2, 1,5	NR	$58-$67	5%	Societal	CP	$112,245
Immunoglobulin vs. No Vaccination											
[135]	Arnal	Age 13/14, Spain	IG	10	700	10 Y: 90%	$21-$31	6%	Societal	CP	$37,562
[135]	Arnal	Age 13/14, Spain	IG	10	4000	10 Y: 90%	$21-$31		Societal	CP	$5,832
ADULTS											
Universal vs. No Vaccination											
[137]	Rajan	Gen pop. age 10-29,Ireland	HA	10	15	10y	$98	5%	NR	CP	$195,634
[83]	OConnor	Healthy adults, U.S.	HA	50	5	20 y: 99%	$79	3%	societal	LY	$591,238
Universal vs. Targeted											
[87]	Bauch	Adult, Canada	HA/HB	lifetime	3.7	Ann. decline 1.7%-3.2%	$27-$50	5%	societal	QALY	$7,986,400
[87]	Bauch	Adult, Canada	HA/HB	lifetime	3.7	Ann. decline 1.7%-3.2%	$27-$50	5%	HS	QALY	$9,871,200
Universal vs. Screen + Vaccinate											
[83]	O'Connor	Healthy adults, U.S.	HA	50	5	20 y: 99%	$79	3%	societal	LY	$34,662,029
Immunoglobulin vs. No Vaccination											
[137]	Raian	Gen pop. age 10-29,Ireland	IG	10	15	10y	$50	5%	NR	CP	$399,337
TARGETED											
TRAVELERS											
Vaccination vs. No Vaccination											
[138]	Severo	Tourists, France	HA	10	36.1	1 y for 2/3 doses	$66	5%	societal	CP	$89,309
[139]	VanDoor-slaer	Travelers, Netherlands	HA	10	Travel to various: 3, 10, 50	10y	$37-$56	5%	NR	CP	$18,660
[139]	VanDoor-slaer	Travelers, Netherlands	HA	10	Travel to various: 3, 10, 50	10y	$37-$56	5%	NR	CP	$25,113

[140]	Tormans	Travelers, Europe	HA	10	3600 (attack rate)	10y	$44	5%	NR	CP	$8,918
Immunoglobulin vs. No Vaccination											
[139]	VanDoor-slaer	Travelers, Netherlands	IG	10	Travel to various: 3, 10, 50	10y	$37-$56	5%	NR	CP	$26,979
[140]	Tormans	Travelers, Europe	IG	10	3600 (attack rate)	10y	$44	5%	NR	CP	$56,831
ADULTS											
HA/HB Vaccination vs. No Vaccination											
[141]	Jacobs	College students, U.S.	HA/HB	70	NR	0.5% annual loss (1-10 Y), 1% (10+ Y)	$41-$88	3%	societal	QALY	<SO
[141]	Jacobs	College students, U.S.	HA/HB	70	NR	0.5% annual loss (1-10 Y), 1% (10+ Y)	$41-$88	3%	HS	QALY	$9,619
Immunoglobulin vs. No Vaccination											
[135]	Arnal	FIR young adults, Spain	IG	10	700	10 Y: 90%	$21	6%	societal	CP	$18,258
[135]	Arnal	FIR adults, Spain	IG	10	700	10 Y: 90%	$21	6%	societal	CP	$7,360
[135]	Arnal	FIR young adults, Spain	IG	10	4000	10 Y: 90%	$21	6%	societal	CP	$3,501
[135]	Arnal	FIR adults, Spain	IG	10	4000	10 Y: 90%	$21	6%	societal	CP	$3,057
INFANTS											
HA vaccination vs. Immunoglobulin											
[122]	Postma	infants of ethnic minorities,Europe	HA	5	NR	10 Y: 90%	$22	4%	societal	CP	$15
HEALTHCARE WORKERS											
Vaccination vs. No Vaccination											
[137]	Rajan	Hospital workers, Ireland	HA	10	15	10 y	$98	5%	societal	CP	$129,757
[99]	Smith	Medical students, US	HA	lifetime	Age (0-60): 320, 71, 44, 42, 40,47,37,20,11	10,30,50y: 95%,81%,74%	$52	3%	societal	QALY	$64,750
[99]	Smith	Medical students, U.S.	HA	lifetime	Age (0-60): 320, 71, 44, 42,40,47,37,20,11	10, 30, 50 y: 95%, 81%,74%	$52	3%	societal	LY	$79,905
[138]	Severo	Hospital workers, France	HA	lifetime	Age (0-60): 320, 71, 44, 42,40,47,37,20,11	10, 30, 50 y: 95%, 81%,74%	$52	3%	societal	CP	$34,634
[142]	Jacobs	Healthcare and public safetyworkers, U.S.	HA/HB	lifetime	(Age 25-75+): 29,22, 15,10, 7,5,4, 3,2,2, 1	10, 30, 50 years 95%,81%,74%	$23	3%	employer	QALY	<$0
Vaccination vs. Immunoglobulin											
[127]	Chodick	Physicians (age 40+), Israel	HA	20	54 (attack rate)	20y	$40	3%	HS	QALY	$114,087
[127]	Chodick	Nursewage 40+), Israel	HA	20	90 (attack rate)	20y	$40	3%	HS	QALY	$375,200
[127]	Chodick	Nursewage 18-39), Israel	HA	20	66 (attack rate)	20y	$40	3%	HS	QALY	$779,596
[127]	Chodick	Physicians (age 18-39), Israel	HA	20	103.55 (attack rate)	20y	$40	3%	HS	QALY	$121,992
[127]	Chodick	Paramedical (age 18-39), Israel	HA	20	113.9 (attack rake)	20y	$40	3%	HS	QALY	$103,023
[127]	Chodick	Paramedical (age 40+), Israel	HA	20	222.5 (attack rake)	20y	$40	3%	HS	QALY	$114,814
Immunoglobulin vs. No Vaccination											
[137]	Rajan	Hospital workers, Ireland	IG	10	15	10y	$50	5%	NR	CP	$265,241
MILITARY											
Universal vs. No Vaccination											
[143]	Buma	Military, Netherlands	HA	NR- 10?	10000 (attack rake)	10y	$54	5%	NR	CP	<$0
[144]	Jefferson	Military (5 deployments), U.K.	HA	5	21	NR	$24	3%	TPP	CP	$109,968
[90]	Jefferson	Military (5 deployments), U.K.	HA	5	200	NR	$24	3%	TPP	CP	$11,474
Universal combined vaccine vs. Screen and vaccinate											
[145]	Jakiche	US Veterans with HCV	HA/HB	complete Vacc. Period	/	100%	$34,05	NR	payer	CP	$154.36
Immunoglobulin vs. No Vaccination											
[143]	Buma	Military, Netherlands	IG	NR- 10?	10000 (attack rake)	10 y	$54	5%	NR	CP	$542

[144]	Jefferson	Military (5 deployments), U.K.	IG	5	21	NR	$24	3%	TPP	CP	$202,411
[144]	Jefferson	Military (5 deployments), U.K.	IG	5	200	NR	$24	3%	TPP	CP	$21,187
PRISON INMATES											
Vaccination HA/HB vs. 11B											
[146]	Jacobs	prison inmates, U.S.	HA/HB	50	(age 5-75): 40,60, 50,40,30, 30, 20, 20, 10, 10	0.5% annual loss (1-10Y), 1% (10+ Y)	$13	3%	HS	LY	$26,093
[146]	Jacobs	prison inmates, U.S.	HA/HB	50	(age 5-75): 111, 150, 120,90,60,60,40,40,30,30	0.5% annual loss (1-10Y), 1% (10+ Y)	$13	3%	HS	LY	$2,416
[146]	Jacobs	prison inmates, U.S.	HA/HB	50	(age 5-75): 170,240, 200,150, 100, 100, 60, 50, 40, 30	0.5% annual loss (1-10y), 1% (10+ y)	$13	3%	HS	LY	<$0
FOOD SERVICE WORKERS											
Vaccination vs. No Vaccination											
[147]	Jacobs	Food service workers, U.S.	HA	45	157	10, 30, 50 y: 95%, 80%,74%	$59	3%	HS	LY	<$0
[147]	Jacobs	Food service workers, U.S.	HA	45	157	10, 30, 50 y: 95%, 80%,74%	$59	3%	HS	LY	$19,245
PATIENTS ATTENDING STD CLINIC											
HA/HB Vaccination vs. HB											
[148]	Jacobs & Meyerhoff	STD, clinic patients, U.S.	HA/HB	50	(Age 18-79): 11.7,16, 17.2,14.3, 10.7, 7.9, 6.2, 5.3, 4.3,3.6, 3.2, 3, 2.9	10, 30, 50 y: 95%, 80%,74%	$13	3%	HS	QALY	$15,161
[148]	Jacobs & Meyerhoff	STD, clinic patients, U.S.	HA/HB	50	(Age 18-79): 11.7,16, 17.2,14.3, 10.7, 7.9, 6.2, 5.3, 4.3,3.6, 3.2, 3, 2.9	10, 30, 50 y: 95%, 80%,74%	$13	3%	HS	LY	$23,642
PATIENTS WITH CHRONIC HEPATITIS C											
Vaccination vs. Screen + Vaccinate											
[149]	Arguedas	HCV, U.S.	HA	lifetime	10	lifetime protection	$62	3%	societal	QALY	$5,029,850
[149]	Arguedas	HCV, U.S.	HA	lifetime	10	lifetime protection	$62	3%	societal	LY	$4,384,997
SECONDARY CASES, CONTACTS											
Vaccination vs. No Vaccination											
[98]	Pechevis	Daycare contacts, France	HA	1	(Age 1-50):7000,7000,6000,5000,4000,2000,0	1 y: 79%	NR	none	HS	CP	<$0
[98]	Pechevis	Nursery school contacts, France	HA	1	(Age 1-50):7000,7000,6000,5000,4000,2000,0	1 y: 79%	NR	none	HS	CP	<$0
[98]	Pechevis	Primary school contacts, France	HA	1	(Age 1-50):7000,7000,6000,5000,4000,2000,0	1 y: 79%	NR	none	HS	CP	<$0
[98]	Pechevis	Household contacts, age 1-49	HA	1	(Age 1-50):7000,7000,6000,5000,4000,2000,0	1 year: 79%	NR	none	HS	CP	$800
[98]	Pechevis	Age 1-14, secondary household cases, France	HA	1	(Age 1-50):7000,7000,6000,5000,4000,2000.0	1 v: 79%	NR	none	HS	CP	$1,551
OTHER											
INFANTS											
Screen+vaccinate vs.No Vaccination											
[130]	Das	Infants, developed countries	HA	lifetime	10	12% ann. Decline of vaccine-induced antibody	$45-	3%	societal	QALY	$9,373
CHILDREN / PRE / ADOLESCENTS											
Screen+vacrinate vs. No Vaccination											
[135]	Arnal	Age 13/14, Spain, low incidence	HA	10	700	10 Y: 90%	$21-$31	6%	societal	CP	$13,344
[135]	Arnal	Age 13/14, Spain, high incidence	HA	10	4000	10 Y: 90%	$21-$31	6%	societal	CP	<$O
ADULTS/ GENERAL POPULATION											

Screen+vacrinate vs. No Vaccination											
[83]	O'connor	Healthy adults, U.S.	HA	50	5	20 y: 99%	$79	3%	societal	LY	$316,474
[137]	Rajan	Gen pop age 10 29, Ireland	HA	10	15	10 Y	$98	5%	NR	CP	$200,941
[135]	Arnal	FIR young adults, Spain	HA	10	700	10 Y: 90%	$21	6%	societal	CP	$4,508
[135]	Arnal	FIR adults, Spain	HA	10	700	10 Y: 90%	$21	6%	societal	CP	$5,946
[135]	Arnal	FIR young adults, Spain	HA	10	4000	10 Y: 90%	$21	6%	societal	CP	<$O
[135]	Arnal	FIR adults, Spain	HA	10	4000	10 Y: 90%	$21	6%	societal	CP	<$O
Screen + Immunoglobulin vs. No Vaccination											
[137]	Rajan	Gen pop age 10 29, Ireland	IG	10	15	10 Y	$50	5%	NR	CP	$306,441
TRAVELERS											
Screen + Vaccinate vs. No Vaccination											
[140]	Tormans	Travelers, Europe	HA	10	3600 (attack rate)	10 Y	$44	5%	NR	CP	$10,271
[138]	Severo	Tourists, France	HA	10	36.1	1 y for 2/3 doses	$66	5%	NR	CP	$55,978
[139]	VanDoor-slaer	Travelers, Netherlands	HA (2dose)	10	Travel to various: 3, 10, 50	10 Y	$37-$56	5%	NR	CP	$20,553
[139]	VanDoor-slaer	Travelers, Netherlands	HA (3 dose)	10	Travel to various: 3, 10, 50	10 Y	$37-$56	5%	NR	CP	$26,559
HEALTHCARE WORKERS											
Screen + Vaccinate vs. No Vaccination											
[99]	Smith	Medical students, U.S.	HA	lifetime	Age (0-60): 320, 71, 44, 42,40,47,37,20,11	10, 30, 50 y: 95%, 8 1%,74%	$52	3%	societal	QALY	$103,325
[99]	Smith	Medical students, U.S.	HA	lifetime	Age (0-60): 320, 71, 44, 42,40,47,37,20,11	10, 30, 50 y: 95%, 8 1%,74%	$52	3%	societal	LY	$126,745
[138]	Severo	Hospital workers, France	HA	lifetime	Age (0-60): 320, 71, 44, 42,40,47,37,20,11	10, 30, 50 y: 95%, 8 1%,74%	$52	3%	societal	CP	$19,033
[137]	Rajan	Hospital workers, Ireland	HA	10	15	10 y	$98	5%	societal	CP	$133,591
Screen + Vaccinate vs. Immunoglobulin											
[127]	Chodick	Physicians (age 40+), Israel	HA	20	54 (attack rate)	20 y: 95%	$40	3%	HS	QALY	$62,882
[127]	Chodick	Physicians (age 18-39), Israel	HA	20	103.55 (attack rate)	20 y: 95%	$40	3%	HS	QALY	$92,414
[127]	Chodick	Nursewage 18-39), Israel	HA	20	66 (attack rate)	20 y: 95%	$40	3%	HS	QALY	$175,255
[127]	Chodick	Nursewage 40+), Israel	HA	20	90 (attack rate)	20 y: 95%	$40	3%	HS	QALY	$106,602
[127]	Chodick	Paramedical (age 18-39), Bract	HA	20	113.9 (attack rate)	20 y: 95%	$40	3%	HS	QALY	$81,204
[127]	Chodick	Paramedical (age 40+), Israel	HA	20	222.5 (attack rate)	20 y: 95%	$40	3%	HS	QALY	$62,731
[137]	Rajan	Hospital workers, Ireland	HA	10	15	10 y	$50	5%	NR	CP	$203,913
PATIENTS WITH CHRONIC HEPATITIS C											
Screen + vaccinate vs. No Vaccination											
[150]	Jacobs	HCV, age 30, US	HA	NR	(Age 30-70): 67, 50, 41,32,35,29,30,26,32	Ann. loss 0.31%-0.62%	$51	3%	societal	LY	$16,386
[150]	Jacobs	HCV, age 45, US	HA	NR	(Age 30-70): 67, 50, 41,32,35,29,30,26,32	Ann. loss 0.31%-0.62%	$51	3%	societal	LY	$51,623
[150]	Jacobs	HCV, age 65, U.S.	HA	NR	(Age 30-70): 67, 50, 41,32,35,29,30,26,32	Ann. loss 0.31%-0.62%	$51	3%	societal	LY	$121,015
[149]	Arguedas	HCV, U.S.	HA	lifetime	10	lifetime	$62	3%	societal	QALY	$65,775
[149]	Arguedas	HCV, U.S.	HA	lifetime	10	lifetime	$62	3%	societal	LY	$58,037
[150]	Jacobs	HCV, age 30, U.S.	HA	NR	(Age 30-70): 67, 50, 41,32,35,29,30,26,32	Ann. loss 0.31%-0.62%	$51	3%	HS	LY	$27,581
[150]	Jacobs	HCV, age 45, U.S.	HA	NR	(Age 30-70): 67, 50, 41,32,35,29,30,26,32	Ann. loss 0.31%-0.62%	$51	3%	HS	LY	$62,448
[150]	Jacobs	HCV, age 65, U.S.	HA	NR	(Age 30-70): 67, 50, 41,32,35,29,30,26,32	Ann. loss 0.31%-0.62%	$51	3%	HS	LY	$126,484
[97]	Myers	HCV, North America	HA	5	10	94% 5-15 y+	$53	NR	TPP	CP	$479,024
[97]	Myers	HCV, North America	HA	5	10	94% 5-15 y+	$53	NR	TPP	Death Prevented	$25,802,250
MILITARY											
Screen + Vaccinate vs. No Vaccination											
[143]	Buma	Military Netherlands	HA	NR- 10?	10000 (attack rate)	10 y	$54	5%	NR	CP	<$O

3. Review of Cost-benefit Analysis of Hepatitis A vaccination

Table 77: Summary of cost-benefit studies

First author	Population studied	Year	Method	Prophylaxis	Time horizon	Annual incidence (per 100 000)	Vaccine price	Discount rate	Perspective	Indirect costs included	Intangible costs included	Benefit-cost ratio
Teppakdee [151]	1- 40 year olds in Thailand	2002	Model	HA vaccine	N.R.	0.79-55	N.R	N.R	payer	no	no	0.1-0.5
Gutersohn [152]	Swissair aircrews	1996	Retrospective analysis	HA vaccine	N.R	153	$50	N.R	Airline company	yes	no	([25])
Mann [153]	House-hold contacts of patients, US	1982	Retrospective analysis	IG	N.R	95.9	N.R	N.R	Payer	no	no	4.89
Jefferson[154]	UN Troups Yougoslavia	1994	Retrospective analysis	HA vaccine	N.R	40-80	$22.26	8%	army	yes	yes	<1
Gillis [155]	Israel defence forces	2000	Retrospective analy-sis	HA/IG	20 years	600-2000	$16	N.R	societal	yes	no	>1([26])
Egoz [128]	Israel (children & pregnant women)	1986	Estimations on public-shed data	IG	N.R	N.R	N.R	N.R	societal	yes	No	0.45 /0.28
Ginsberg [156]	Infants Israel	2001	Model	HA	45 years	54	$7.47	4%	Societal /payer	yes	No	2.54/1.8

25 beneficial within 10 years for pilots

26 specified according to incidence rate and type of soldier

APPENDIX C

LIST OF HOSPITAL DIAGNOSES APPEARING WITH 'HEPATITIS A IN SECONDARY DIAGNOSIS'

This table lists, for all hospitalizations related to HAV (in secondary diagnosis) during 2000-2004, the most common other diagnoses made during hospitalization. These diagnoses are described in Dutch and sorted according to the frequency of occurrence. The minimum frequency to be listed in this appendix was arbitrarily set at 10.

frequency	Diagnosis made complementary with 'HAV in secondary diagnosis'
159	DUMMY
140	ESSENTIELE HYPERTENSIE, NIET GESPECIFICEERD
111	TABAKSGEBRUIKSSTOORNIS
98	DIAGNOSE SPOEDGEVALLEN
80	ZUIVERE HYPERCHOLESTEROLEMIE
67	DIABETES MELLITUS ZONDER VERMELDING VAN COMPLICATIE, TYPE II (NIET-INSULINE DEPENDENT) (NIDDM-TYPE) ('ADULT-ONSET') OF NIET GESPECIFICEERDE VORM, NIET-GESPECIFICEERD ALS INSTABIEL
65	URINEWEGINFECTIE, LOKALISATIE NIET GESPECIFICEERD
62	ATRIUMFIBRILLEREN
61	VIRUS HEPATITIS B ZONDER VERMELDING VAN HEPATISCH COMA, ACUUT OF NIET-GESPECIFICEERD, ZONDER VERMELDING VAN HEPATITIS DELTA
59	BENIGNE ESSENTIELE HYPERTENSIE
57	OVERIGE EN NIET GESPECIFICEERDE ALCOHOLVERSLAVING, CONTINU
49	ONDERVULLING VAN HET VAATSTELSEL EN DE EXTRACELLULAIRE RUIMTE
46	OVERIGE GESPECIFICEERDE NAZORG NA OPERATIE
46	OBESITAS, NIET-GESPECIFICEERD
44	INFECTIE DOOR ESCHERICHIA COLI -E. COLI- BIJ ELDERS GECLASSIFICEERDE - AANDOENINGEN EN MET NIET GESPECIFICEERDE LOKALISATIE
44	ANEMIE, NIET GESPECIFICEERD
42	OBSTRUCTIEVE CHRONISCHE BRONCHITIS ZONDER EXACERBATIE
40	OVERIGE GESPECIFICEERDE VORMEN VAN CHRONISCHE ISCHEMISCHE HARTAANDOENINGEN
39	VIRUS HEPATITIS B ZONDER VERMELDING VAN HEPATISCH COMA, CHRONISCH, ZONDER VERMELDING VAN HEPATITIS DELTA
39	ALCOHOLISCHE LEVERCIRROSE
38	HERNIA DIAPHRAGMATICA, ZONDER VERMELDING VAN OBSTRUCTIE OF GANGREEN
37	ACUTE NIERINSUFFICIENTIE NIET GESPECIFICEERDE ACUTE NIERINSUFFICIENTIE
37	RISICOFACTOR VOOR DE GEZONDHEID IN DE PERSOONLIJKE ANAMNESE, CHIRURGIE AAN ANDERE BELANGRIJKE ORGANEN
36	CARDIOMEGALIE
35	NIET GESPECIFICEERDE HYPOTHYREOIDIE
34	PERSOONLIJKE ANAMNESE MET ALLERGIE VOOR PENICILLINE
33	DYSTHYMIE
32	MITRAALKLEP AANDOENINGEN
32	RESULTAAT VAN DE BEVALLING, ENKELVOUDIGE LEVEND GEBORENE
32	OESOFAGITIS, NIET-GESPECIFICEERD
32	ASCITES
32	HYPOKALIEMIE
31	OBSTRUCTIEVE CHRONISCHE BRONCHITIS MET (ACUTE) EXACERBATIE
31	OUD MYOCARD INFARCT

31	LEVERCIRROSE ZONDER VERMELDING VAN ALCOHOL
30	OVERIGE GESPECIFICEERDE CHRONISCHE NIET-ALCOHOLISCHE LEVERAANDOENINGEN
30	DEPRESSIEVE STOORNIS, NIET ELDERS GECLASSIFICEERD
29	ACUTE HEPATITIS C ZONDER VERMELDING VAN HEPATISCH COMA
29	ULCUS VENTRICULI, NIET GESPECIFICEERD ALS ACUUT OF CHRONISCH, ZONDER BLOEDING OF PERFORATIE, ZONDER OBSTRUCTIE
26	VIRUS HEPATITIS A MET HEPATISCH COMA
26	HYPO-OSMOLALITEIT EN-OF HYPONATRIEMIE
26	ACUTE EN SUBACUTE LEVERCELNECROSE
25	GAL BLAAS STEEN ZONDER VERMELDING VAN CHOLECYSTITIS, ZONDER VERMELDING VAN OBSTRUCTIE
25	PERSOONLIJKE ANAMNESE MET ULCUS PEPTICUM AANDOENING
25	EEN ORGAAN OF WEEFSEL DAT OP EEN ANDERE WIJZE DAN TRANSPLANTATIE VERVANGEN IS, HEUP
25	OVERIGE EN NIET GESPECIFICEERDE ANGINA PECTORIS
25	NIET-SPECIFIEKE VERHOGING VAN DE SPIEGELS VAN TRANSAMINASE OF MELKZUURDEHYDROGENASE -LDH-
25	CORONAIRE ATHEROSCLEROSE VAN OORSPRONKELIJKE CORONAIRE ARTERIE
24	NIET GESPECIFICEERDE TROMBOCYTOPENIE
24	CHRONISCHE NIERINSUFFICIENTIE
24	POSTOPERATIEVE TOESTAND, AORTOCORONAIRE BYPASS STATUS
24	NIET GESPECIFICEERD ASTMA NIET GESPECIFICEERD
23	NIET GESPECIFICEERDE OSTEOPOROSE
23	OVERIGE AFWIJKENDE BLOEDCHEMIE
22	KOORTS
22	OVERIGE EN NIET GESPECIFICEERDE VORMEN VAN HYPERLIPIDEMIE
22	PORTALE HYPERTENSIE
22	CHRONISCHE HEPATITIS C ZONDER VERMELDING VAN HEPATISCH COMA
22	DIABETES MELLITUS ZONDER VERMELDING VAN COMPLICATIE, 'ADULT-ONSET' OF NIET GESPECIFICEERDE VORM, INSTABIEL
21	RISICOFACTOR VOOR DE GEZONDHEID IN DE PERSOONLIJKE ANAMNESE, ANAMNESE MET TABAKSGEBRUIK
21	PNEUMONIE, VERWEKKER NIET GESPECIFICEERD
21	HEPATISCH COMA
21	AORTAKLEP AANDOENINGEN
21	OVERIGE LONGINSUFFICIENTIE, NIET ELDERS GECLASSIFICEERD
21	ACUTE POSTHEMORRAGISCHE ANEMIE
21	REFLUXOESOFAGITIS
20	PERSOONLIJKE ANAMNESE MET OVERIGE ZIEKTEN VAN HET SPIJSVERTERINGSKANAAL
20	OEDEEM
19	DECUBITUS ULCUS
19	ANOREXIE
19	ALLEENWONENDE
19	OVERIGE GESPECIFICEERDE REVALIDATIE PROCEDURES
19	BRONCHOPNEUMONIE, VERWEKKER NIET GESPECIFICEERD
19	CONGESTIEF HARTFALEN NIET GESPECIFIEERD
19	ASYMPTOMATISCHE VARICOSE ADERS ONDERSTE EXTREMITEITEN
18	OVERIGE GESPECIFICEERDE VORMEN VAN GASTRITIS ZONDER VERMELDING VAN BLOEDING

18	PERSOONLIJKE ANAMNESE MET ALLERGIE VOOR OVERIGE GESPECIFICEERDE GENEESMIDDELEN
18	OVERIGE GESPECIFICEERDE AANDOENINGEN VAN DE LEVER
18	NIET GESPECIFICEERDE VOCHTOPHOPING IN DE PLEURA
17	ACUTE BRONCHITIS
17	OVERIGE GESPECIFICEERDE SHOCK
17	NIET GESPECIFICEERDE IJZERGEBREKSANEMIE
16	STREPTOKOKKEN GROEP D (ENTEROCOCCUS)
16	ALLEEN BRAKEN
16	STAFYLOCOCCUS AUREUS
16	OVERIGE OESOFAGITIS
16	ACUTE PANCREATITIS
16	OVERIGE GESPECIFICEERDE STOORNISSEN VAN HET PLASMA PROTEINE METABOLISME
16	DIVERTICULOSE VAN HET COLON ZONDER VERMELDING VAN BLOEDING
15	OVERIGE VIRUSZIEKTEN, BEVALLING
15	METASTASEN IN LEVER, GESPECIFICEERD ALS METASTASE
15	OVERIGE GRAM-NEGATIEVE ORGANISMEN
15	NIET GESPECIFICEERDE CEREBRALE DEGENERATIE
15	HERNIA NUCLEI PULPOSI LUMBALIS ZONDER MYELOPATHIE
15	OESOFAGUS VARICES BIJ ELDERS GECLASSIFICEERDE ZIEKTEN, ZONDER VERMELDING VAN BLOEDING
15	BEHOEFTE AAN ISOLATIE
15	OVERIGE MALAISE EN VERMOEIDHEID
14	MONONUCLEOSIS INFECTIOSA
14	OSTEO-ARTROSE, GELOKALISEERD, ZONDER SPECIFICATIE VAN PRIMAIR OF SECUNDAIR, BEKKENSTREEK EN BOVENBEEN
14	NIET GESPECIFICEERDE HEPATITIS
14	NIET GESPECIFICEERDE VITAMINE D DEFICIENTIE
14	ANDERE GESPECIFICEERDE VORMEN VAN VOCHT IN DE PLEURA, BEHALVE TUBERCULOSE
14	NIET GESPECIFICEERDE PERIFERE VENEUZE INSUFFICIENTIE
14	GAL BLAAS STEEN MET ANDERE VORMEN VAN CHOLECYSTITIS, ZONDER VERMELDING VAN OBSTRUCTIE
14	INFECTIE DOOR BACIL VAN FRIEDLAENDER BIJ ELDERS GECLASSIFICEERDE AANDOENINGEN EN MET NIET GESPECIFICEERDE LOKALISATIE
14	HARTSTILSTAND
14	MORBIEDE OBESITAS
14	EEN ORGAAN OF WEEFSEL DAT OP EEN ANDERE WIJZE DAN TRANSPLANTATIE VERVANGEN IS, KNIE
14	BLOEDING ALS COMPLICATIE VAN EEN VERRICHTING
13	HERNIA INGUINALIS, ZONDER VERMELDING VAN OBSTRUCTIE OF GANGREEN, ENKELZIJDIG OF NIET GESPEC. NIET GESPEC. ALS RECID.
13	OVERIGE EN NIET GESPECIFICEERDE ALCOHOLVERSLAVING, NIET GESPECIFICEERD
13	AGRANULOCYTOSE
13	AFSLUITING EN STENOSE VAN ARTERIA CAROTIS, ZONDER VERMELDING VAN INFARCT VAN HERSENEN
13	NIET GESPECIFICEERDE GASTRITIS EN GASTRODUODENITIS ZONDER VERMELDING VAN BLOEDING
13	POLYNEUROPATHIE BIJ DIABETES
13	GELEIDINGSSTOORNISSEN, RECHTER BUNDELTAK BLOCK
13	ULCUS VAN DE OESOFAGUS
13	EPILEPSIE NNO, MET VERMELDING VAN ONBEHANDELBAARHEID

13	NIERCYSTE, VERWORVEN
13	ATHEROSCLEROSE VAN OORSPRONKELIJKE ARTERIES VAN LEDEMATEN, NIET-GESPECIFICEERD
13	OVERIGE GESPECIFICEERDE AANDOENINGEN VAN DE GALWEGEN
13	HUMAN IMMUNODEFICIENCY VIRUS -HIV- ZIEKTE
13	HEPATOMEGALIE
13	PARALYSIS AGITANS
13	ZORG WAARBIJ REVALIDATIE PLAATS VINDT, OVERIGE VORMEN VAN FYSISCHE THERAPIE
13	DIARREE
13	GEWICHTSVERLIES
13	PERCUTANE TRANSLUMINALE CORONAIRE ANGIOPLASTIE STATUS
12	CACHEXIE
12	GEELZUCHT, NIET GESPECIFICEERD, NIET VAN DE PASGEBORENE
12	NIET GESPECIFICEERDE NIERINSUFFICIENTIE
12	OVERIGE GESPECIFICEERDE HART DYSRITMIEEN
12	PSEUDOMONAS
12	TRICUSPIDAALKLEP AANDOENINGEN, GESPECIFICEERD ALS NIET-REUMATISCH
12	ATROFISCHE GASTRITIS ZONDER VERMELDING VAN BLOEDING
12	OVERIGE EN NIET GESPECIFICEERDE NIET-INFECTIEUZE GASTRO-ENTERITIS EN COLITIS
12	HARTDECOMPENSATIE, LINKSDECOMPENSATIE
12	OVERIGE CHRONISCHE PULMONALE HARTAANDOENINGEN
12	ADENOCARCINOOM NNO
12	OVERIGE GESPECIFICEERDE ADEMHALINGSSTOORNISSEN
12	ANGSTTOESTAND, NIET GESPECIFICEERD
11	MALIGNE NEOPLASMA VAN DE VROUWELIJKE BORST, NIET GESPECIFICEERD
11	POSTOPERATIEVE TOESTAND, HART PACEMAKER IN SITU
11	HYPERKALIEMIE
11	SYNCOPE EN COLLAPS
11	THYREOTOXICOSE ZONDER VERMELDING VAN STRUMA OF ANDERE OORZAAK, ZONDER VERMELDING VAN CRISIS
11	SPLENOMEGALIE
11	VERSLAVING AAN OPIATEN EN DERGELIJKE, CONTINU
11	'INTERMEDIATE' CORONAIR SYNDROOM
11	OSTEO-ARTROSE, GELOKALISEERD, PRIMAIR, ONDERBEEN
11	OVERIGE STAFYLOKOKKEN
11	SENIELE OSTEOPOROSE
11	ALCOHOLISCHE VETLEVER
11	NIET-GESPECIFICEERDE VAL
11	MALAISE EN VERMOEIDHEID
10	HOOFDPIJN
10	OBSTIPATIE
10	CEREBRALE ATHEROSCLEROSE
10	SEPSIS DOOR ESCHERICHIA COLI -E. COLI-
10	URINERETENTIE, NIET-GESPECIFICEERD
10	ATRIUM 'FLUTTER' -FLADDEREN-
10	LEVERAANDOENING IN DE ZWANGERSCHAP, BEVALLING
10	ATHEROSCLEROSE VAN AORTA
10	ZIEKTE VAN ALZHEIMER

10	OESOFAGALE REFLUX
10	ALCOHOLISCHE POLYNEUROPATHIE
10	ACIDOSE
10	PERSOONLIJKE ANAMNESE MET OVERIGE ZIEKTEN VAN HART- EN VAATSTELSEL
10	OVERIGE ALLERGIE, BEHALVE DIE VOOR GENEESMIDDELEN
10	ONVOLDOENDE MATERIELE HULPBRONNEN

APPENDIX D

REGIONS AND AREACODES

The following table shows the different areacodes ('arrondissementscodes') and the region to which this area was attributed.

1. Flanders

Code_arrond	Label_FR	Label_NL
11	Anvers	Antwerpen
12	Malines	Mechelen
13	Turnhout	Turnhout
23	Hal-Vilvorde	Halle-Vilvoorde
24	Louvain	Leuven
31	Bruges	Brugge
32	Dixmude	Diksmude
33	Ypres	Ieper
34	Courtrai	Kortrijk
35	Ostende	Oostende
36	Roulers	Roeselaer
37	Tielt	Tielt
38	Furnes	Veurne
41	Alost	Aalst
42	Termonde	Dendermonde
43	Eeklo	Eeklo
44	Gand	Gent
45	Audenarde	Oudenaarde
46	Saint-Nicolas	Sint-Niklaas
71	Hasselt	Hasselt
72	Maaseik	Maaseik
73	Tongres	Tongeren

2. Brussels (Brussels hoofdstedelijk gewest)

Code_arrond	Label_FR	Label_NL
21	Bruxelles-Capitale	Brussels Hoofdstedelijk Gewest

3. Wallonia

Code_arrond	Label_FR	Label_NL
25	Nivelles	Nijvel
51	Ath	Aat
52	Charleroi	Charleroi
53	Mons	Bergen
54	Mouscron	Moeskroen
55	Soignies	Zinnik
56	Thuin	Thuin
57	Tournai	Doornik
61	Huy	Hoei
62	Liège	Luik
63	Verviers	Verviers
64	Waremme	Borgworm
81	Arlon	Aarlen
82	Bastogne	Bastenaken
83	Marche-en-Famenne	Marche-en-Famenne
84	Neufchâteau	Neufchâteau
85	Virton	Virton
91	Dinant	Dinant
92	Namur	Namen
93	Philippeville	Philippeville

6 REFERENCES

1. Hendrickx, G., et al., Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology. J Viral Hepat, 2008. **15 Suppl 2**: p. 1-15.
2. Van Herck, K. and P. Van Damme, Prevention of hepatitis A by Havrix : a review. Expert Review of Vaccines, 2005. **4**(4): p. 459-471.
3. Andre, F., et al., Inactivated hepatitis A vaccine: immunogenicity, efficacy, safety and review of official recommendations for use. Expert Rev Vaccines, 2002. **1**(1): p. 9-23.
4. Werzberger, A., et al., A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children [see comments]. The New England Journal of Medicine, 1992. **327**(7): p. 453-457.
5. Werzberger, A., et al., Effectiveness of hepatitis A vaccine in a former frequently affected community: 9 years' followup after the Monroe field trial of VAQTA(R). Vaccine, 2002. **20**(13-14): p. 1699-1701.
6. Nalin, D.R., et al., Worldwide experience with the CR326F-derived inactivated hepatitis A virus vaccine in pediatric and adult populations: an overview. J.Hepatol., 1993. **18 Suppl 2**: p. S51-S55.
7. Loutan, L., et al., Inactivated Virosome Hepatitis-A Vaccine. Lancet, 1994. **343**(8893): p. 322-324.
8. Ambrosch, F., et al., Rapid Antibody Response after Vaccination with a Virosomal Hepatitis A Vaccine. Infection, 2004. **32**(3): p. 149-152.
9. Bovier, P.A., et al., Long-term immunogenicity of an inactivated virosome hepatitis A vaccine. J.Med.Virol., 2002. **68**(4): p. 489-493.
10. Vidor, E., et al., Aventis Pasteur vaccines containing inactivated hepatitis A virus: a compilation of immunogenicity data. Eur.J.Clin.Microbiol.Infect.Dis., 2004. **23**(4): p. 300-309.
11. Dagan, R., et al., Safety and immunogenicity of a new formulation of an inactivated hepatitis A vaccine. Vaccine, 1999. **17**(15-16): p. 1919-1925.
12. Mao, J.S., et al., Further evaluation of the safety and protective efficacy of live attenuated hepatitis A vaccine (H2-strain) in humans. Vaccine, 1997. **15**(9): p. 944-947.
13. Rader, R., Hepatitis A vaccine products in Biopharmaceutical products in the US and European markets, in Accessed at http://www.biopharma.com/hep_a_vaccines.pdf, R. Bioplan Associates, Editor. 2005. p. 557.
14. Minutello, M., et al., Dose range evaluation of a new inactivated hepatitis A vaccine administered as a single dose followed by a booster. Vaccine, 2000. **19**(1): p. 10-15.
15. Van Damme, P. and K. Van Herck, A review of the efficacy, immunogenicity and tolerability of a combined hepatitis A and B vaccine. Expert Rev.Vaccines, 2004. **3**(3): p. 249-267.
16. Beran, J., et al., A Single Dose, Combined Vaccine against Typhoid Fever and Hepatitis A: Consistency, Immunogenicity and Reactogenicity. Journal of Travel Medicine, 2000. **7**(5): p. 246-252.
17. Merck, Indication for VAQTA (hepatitis A Vaccine, inactivated), Merck's Hepatitis A Vaccine, to children as young as 12 months of age, in Accessed at http://www.merck.com/newsroom/press_releases/products/2005_0815.html, 8 November 2005. 2005.
18. Glaxosmithkline, Havrix (Hepatitis A vaccine, inactivated). Prescribing information. Accessed at http://us.gsk.com/products/assets/us_havrix.pdf, 8 November 2005. 2005.
19. Hanna, J.N., S.L. Hills, and J.L. Humphreys, Impact of hepatitis A vaccination of Indigenous children on notifications of hepatitis A in north Queensland. Medical Journal of Australia, 2004. **181**(9): p. 482-485.
20. Bell, B.P. and S.M. Feinstone, Hepatitis A Vaccine, in Vaccines, S. Plotkin and W.A. Orenstein, Editors. 2004, W.B. Saunders Company: Philadelphia. p. 269-297.
21. Tilzey, A.J., et al., Hepatitis A vaccine responses in HIV-positive persons with haemophilia. Vaccine, 1996. **14**(11): p. 1039-1041.
22. Linglof, T., et al., An open study of subcutaneous administration of inactivated hepatitis A vaccine (VAQTA(R)) in adults: safety, tolerability, and immunogenicity. Vaccine, 2001. **19**(28-29): p. 3968-3971.

23. Fisch, A., et al., Immunogenicity and safety of a new inactivated Hepatitis A Vaccine: a clinical trial with comparison of administration route. Vaccine, 1996. **14**(12): p. 1132-1136.
24. Stephen, R., et al. Subcutaneous versus intramuscular administration of a virosome formulated hepatitis A vaccine. in 10th Eur. Congr. Clin Microbiol Infect Dis.(ECCMID). 2000. Stockholm.
25. WHO, Hepatitis A vaccines WHO position paper. Weekly Epidemiological Record, 2000. **75**: p. 38-44.
26. Black, S., et al., A post-licensure evaluation of the safety of inactivated hepatitis A vaccine (VAQTA(R), Merck) in children and adults. Vaccine, 2004. **22**(5-6): p. 767-773.
27. Zuckerman, J., et al., Comparison of the safety and immunogenicity of two inactivated hepatitis A vaccines. Advances in Therapy, 1997. **14**: p. 116-124.
28. Bovier, P.A., T. Farinelli, and L. Loutan, Interchangeability and tolerability of a virosomal and an aluminum-adsorbed hepatitis A vaccine. Vaccine, 2005. **23**(19): p. 2424-2429.
29. Clarke, P.D., et al. Rate, intensity, and duration of local reactions to a virosome-adjuvanted versus an aluminium -absorbed hepatitis A vaccine in UK travellers. in 9th Conference of the International Society of Travel Medecine (9th CISTM). 2005. Lisbon.
30. Huang, D.B., J.J. Wu, and S.K. Tyring, A review of licensed viral vaccines, some of their safety concerns, and the advances in the development of investigational viral vaccines. Journal Of Infection, 2004. **49**(3): p. 179-209.
31. Purcell, R.H., et al., Inactivated hepatitis A vaccine: active and passive immunoprophylaxis in chimpanzees. Vaccine, 1992. **10 Suppl 1**: p. S148-151.
32. Connor, B.A., K. Van Herck, and P. Van Damme, Rapid protection and vaccination against hepatitis A for travellers. Biodrugs, 2003. **17 Suppl 1**: p. 19-21.
33. Bryan, J.P., et al., Randomized, cross-over, controlled comparison of two inactivated hepatitis A vaccines. Vaccine, 2000. **19**(7-8): p. 743-750.
34. Innis, B.L., et al., Protection against hepatitis A by an inactivated vaccine [see comments]. JAMA: The Journal of the American Medical Association, 1994. **271**(17): p. 1328-1334.
35. Mayorga Perez, O., et al., Efficacy of virosome hepatitis A vaccine in young children in Nicaragua: randomized placebo-controlled trial. J Infect Dis, 2003. **188**(5): p. 671-7.
36. Letson, G.W., et al., Effect of maternal antibody on immunogenicity of hepatitis A vaccine in infants. Journal Of Pediatrics, 2004. **144**(3): p. 327-332.
37. Kanra, G., et al., Clinical trial to evaluate immunogenicity and safety of inactivated hepatitis A vaccination starting at 2-month-old children. Turkish Journal of Pediatrics, 2000. **42**(2): p. 105-108.
38. Piazza, M., et al., Safety and immunogenicity of hepatitis A vaccine in infants: a candidate for inclusion in the childhood vaccination programme. Vaccine, 1999. **17**(6): p. 585-588.
39. Dagan, R., et al., Immunization against hepatitis A in the first year of life: priming despite the presence of maternal antibody. Pediatr.Infect.Dis.J., 2000. **19**(11): p. 1045-1052.
40. Kanra, G., et al., Hepatitis A booster vaccine in children after infant immunization. Pediatric Infectious Disease Journal, 2002. **21**(8): p. 727-730.
41. Fiore, A.E., et al., Hepatitis A vaccination of infants: effect of maternal antibody status on antibody persistence and response to a booster dose. Pediatric Infectious Disease Journal, 2003. **22**(4): p. 354-359.
42. Usonis, V., et al., Antibody titres after primary and booster vaccination of infants and young children with a virosomal hepatitis A vaccine (Epaxal((R))). Vaccine, 2003. **21**(31): p. 4588-4592.
43. Bock, H.L., et al., Does the Concurrent Administration of an Inactivated Hepatitis A Vaccine Influence the Immune Response to Other Travelers Vaccines? Journal of Travel Medicine, 2000. **7**(2): p. 74-78.
44. Jong, E.C., et al., An Open Randomized Study of Inactivated Hepatitis A Vaccine Administered Concomitantly with Typhoid Fever and Yellow Fever Vaccines. Journal of Travel Medicine, 2002. **9**(2): p. 66-70.
45. Bovier, P.A., et al., Tolerance and immunogenicity of the simultaneous administration of virosome hepatitis A and yellow fever vaccines. J.Travel.Med., 1999. **6**(4): p. 228-233.

46. Dumas, R., et al., Safety and immunogenicity of a new inactivated hepatitis A vaccine in concurrent administration with a typhoid fever vaccine or a typhoid fever + yellow fever vaccine. Adv Ther, 1997. **14**(4): p. 160-7.
47. Reuman, P.D., et al., The effect of age and weight on the response to formalin inactivated, alum-adjuvanted hepatitis A vaccine in healthy adults. Vaccine, 1997. **15**(10): p. 1157-1161.
48. D'Acremont, V., C. Herzog, and B. Genton, Immunogenicity and Safety of a Virosomal Hepatitis A Vaccine (Epaxal®) in the Elderly. Journal of Travel Medicine, 2006. **13**(2): p. 78-83.
49. Stoffel, M., et al., Immunogenicity of Twinrix in older adults: a critical analysis. Expert Review of Vaccines, 2003. **2**(1): p. 9-14.
50. Nothdurft, H.D., et al., A breakthrough case of hepatitis A disease following a full vaccination schedule of three doses of a combined hepatitis A and B vaccine. Vaccine, 2004. **22**(5-6): p. 592-3.
51. Stark, K., et al., Immunogenicity and safety of hepatitis A vaccine in liver and renal transplant recipients. J Infect Dis, 1999. **180**(6): p. 2014-7.
52. Gunther, M., et al., Rapid decline of antibodies after hepatitis A immunization in liver and renal transplant recipients. Transplantation, 2001. **71**(3): p. 477-9.
53. Arslan, M., et al., Safety and efficacy of hepatitis A vaccination in liver transplantation recipients. Transplantation, 2001. **72**(2): p. 272-6.
54. Landry, P., et al., Inactivated hepatitis A vaccine booster given >= 24 months after the primary dose. Vaccine, 2000. **19**(4-5): p. 399-402.
55. Iwarson, S., M. Lindh, and L. Widerstrom, Excellent booster response 4 to 8 years after a single primary dose of an inactivated hepatitis A vaccine. Journal of Travel Medicine, 2004. **11**(2): p. 120-121.
56. Williams, J.L., et al., Hepatitis A vaccine: immunogenicity following administration of a delayed immunization schedule in infants, children and adults. Vaccine, 2003. **21**(23): p. 3208-3211.
57. Beck, B.R., et al., Immunogenicity of Booster Vaccination with a Virosomal Hepatitis A Vaccine after Primary Immunization with an Aluminum-adsorbed Hepatitis A Vaccine. Journal of Travel Medicine, 2004. **11**(4): p. 201-207.
58. Van Damme, P., et al., Inactivated hepatitis A vaccine: reactogenicity, immunogenicity, and long-term antibody persistence. J.Med.Virol., 1994. **44**(4): p. 446-451.
59. Wiens, B.L., et al., Duration of protection from clinical hepatitis A disease after vaccination with VAQTA. J Med Virol, 1996. **49**(3): p. 235-241.
60. Fan, P.C., et al., Follow-up immunogenicity of an inactivated hepatitis A virus vaccine in healthy children: results after 5 years. Vaccine, 1998. **16**(2-3): p. 232-235.
61. Van Herck, K., et al. Antibody persistence 10 years after immunisation with a two dose inactivated hepatitis A vaccine. in 11th International Congress on Infectious Diseases. . 2004. Cancun, Mexico.
62. Van Herck, K., et al., Mathematical models for assessment of long-term persistence of antibodies after vaccination with two inactivated hepatitis A vaccines. J Med.Virol., 2000. **60**(1): p. 1-7.
63. Van Damme, P., et al., Hepatitis A booster vaccination: is there a need? Lancet, 2003. **362**(9389): p. 1065-1071.
64. Wasley, A., T. Samandari, and B.P. Bell, Incidence of Hepatitis A in the United States in the Era of Vaccination. JAMA: The Journal of the American Medical Association, 2005. **294**(2): p. 194-201.
65. Averhoff, F., et al., Control of Hepatitis A Through Routine Vaccination of Children. Jama, 2001. **286**(23): p. 2968-2973.
66. Bialek, S.R., et al., Hepatitis A Incidence and Hepatitis A Vaccination Among American Indians and Alaska Natives, 1990-2001. Am J Public Health, 2004. **94**(6): p. 996-1001.
67. Dagan, R., et al., Incidence of Hepatitis A in Israel Following Universal Immunization of Toddlers. JAMA: The Journal of the American Medical Association, 2005. **294**(2): p. 202-210.
68. MacIntyre, C.R., et al., Hepatitis a vaccination options for Australia. Journal of Paediatrics and Child Health, 2003. **39**(2): p. 83-87.

69. Lopalco, P.L., et al., Hepatitis A and B in children and adolescents--what can we learn from Puglia (Italy) and Catalonia (Spain)? Vaccine, 2000. **19**(4-5): p. 470-4.
70. Dominguez, A., et al., Effectiveness of a mass hepatitis A vaccination program in preadolescents. Vaccine, 2003. **21**(7-8): p. 698-701.
71. Van Damme, P. and K. Van Herck, Effect of hepatitis A vaccination programs. JAMA: The Journal of the American Medical Association, 2005. **294**(2): p. 246-248.
72. Robertson, B.H., et al., Effect of postexposure vaccination in a chimpanzee model of hepatitis A virus infection. J Med Virol, 1994. **43**(3): p. 249-51.
73. Sagliocca, L., et al., Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomised trial. The Lancet, 1999. **353**(9159): p. 1136-1139.
74. Furesz, J., D.W. Scheifele, and L. Palkonyay, Safety and effectiveness of the new inactivated hepatitis A virus vaccine. CMAJ., 1995. **152**(3): p. 343-348.
75. Syed, N.A., et al., Outbreak of hepatitis A in the injecting drug user and homeless populations in Bristol: control by a targeted vaccination programme and possible parenteral transmission. Eur J Gastroenterol Hepatol, 2003. **15**(8): p. 901-6.
76. Bonanni, P., et al., Vaccination against hepatitis A during outbreaks starting in schools: what can we learn from experiences in central Italy? Vaccine, 2005. **23**(17-18): p. 2176-2180.
77. Anonychuk, A.M., et al., Cost-Effectiveness Analyses of Hepatitis A Vaccine: A Systematic Review to Explore the Effect of Methodological Quality on the Economic Attractiveness of Vaccination Strategies. Pharmacoeconomics, 2008. **26**(1): p. 17-32.
78. Todd, E.C., Costs of acute bacterial foodborne disease in Canada and the United States. Int J Food Microbiol, 1989. **9**(4): p. 313-26.
79. Berge, J.J., et al., The cost of hepatitis A infections in American adolescents and adults in 1997. Hepatology, 2000. **31**(2): p. 469-73.
80. Tolsma, D.D. and J.A. Bryan, The economic impact of viral hepatitis in the United States. Public Health Rep, 1976. **91**(4): p. 349-53.
81. Hadler, S.C., Global impact of hepatitis A virus infection: changing patterns. In: Hollinger FB, Lemon SM, Margolis H, eds. Viral hepatitis and liver disease. 1991, Baltimore MD: Williams and Williams. 14-19.
82. Jacobs, R.J., H.S. Margolis, and P.J. Coleman, The cost-effectiveness of adolescent hepatitis A vaccination in states with the highest disease rates. Arch Pediatr Adolesc Med, 2000. **154**(8): p. 763-70.
83. O'Connor, J.B., T.F. Imperiale, and M.E. Singer, Cost-effectiveness analysis of hepatitis A vaccination strategies for adults. Hepatology, 1999. **30**(4): p. 1077-81.
84. Dalton, C.B., et al., The cost of a food-borne outbreak of hepatitis A in Denver, Colo. Arch Intern Med, 1996. **156**(9): p. 1013-6.
85. Bownds, L., R. Lindekugel, and P. Stepak, Economic impact of a hepatitis A epidemic in a mid-sized urban community: the case of Spokane, Washington. J Community Health, 2003. **28**(4): p. 233-46.
86. Sansom, S.L., et al., Costs of a hepatitis A outbreak affecting homosexual men - Franklin County, Ohio, 1999. American Journal of Preventive Medicine, 2003. **25**(4): p. 343-346.
87. Bauch, C.T., et al., Cost-utility of universal hepatitis A vaccination in Canada. Vaccine, 2007. **25**(51): p. 8536-48.
88. Tricco, A.C., et al., A review of interventions triggered by hepatitis A infected food-handlers in Canada. BMC Health Serv Res, 2006. **6**: p. 157.
89. Sansom, S.L., et al., Costs of a hepatitis A outbreak affecting homosexual men: Franklin County, Ohio, 1999. Am J Prev Med, 2003. **25**(4): p. 343-6.
90. Demicheli, V., D. Rivetti, and T.O. Jefferson, Economic aspects of a small epidemic of hepatitis A in a religious community in Northern Italy. J Infect, 1996. **33**(2): p. 87-90.
91. Lucioni, C., et al., Cost of an outbreak of hepatitis A in Puglia, Italy. Pharmacoeconomics, 1998. **13**(2): p. 257-66.
92. Taylor-Robinson, D.C., et al., Exploration of cost effectiveness of active vaccination in the control of a school outbreak of hepatitis A in a deprived community in the United Kingdom. Euro Surveill, 2007. **12**(12): p. E5-6.

93. Chossegros, P., et al., [Cost of acute hepatitis A in adults in France]. Presse Med, 1994. **23**(12): p. 561-4.
94. de Juanes, J.R., et al., Cost analysis of two strategies for hepatitis A vaccination of hospital health-care personnel in an intermediate endemicity area. Vaccine, 2001. **19**(30): p. 4130-4134.
95. Diel, R., B. Rappenhoner, and S. Schneider, Cost-effectiveness of hepatitis A immunisation of children and adolescents in Germany. Hepac Health Economics in prevention & Care, 2001. **2**(3): p. 96-103.
96. Jacobs, R.J., et al., Regional variation in the cost effectiveness of childhood hepatitis A immunization. Pediatric Infectious Disease Journal, 2003. **22**(10): p. 904-914.
97. Myers, R.P., J.C. Gregor, and P.J. Marotta, The cost-effectiveness of hepatitis A vaccination in patients with chronic hepatitis C. Hepatology, 2000. **31**(4): p. 834-839.
98. Pechevis, M., et al., Cost-effectiveness of hepatitis A vaccine in prevention of secondary hepatitis A infection. Vaccine, 2003. **21**(25-26): p. 3556-3564.
99. Smith, S., et al., Cost-effectiveness of hepatitis A vaccination in healthcare workers. Infection Control and Hospital Epidemiology, 1997. **18**(10): p. 688-691.
100. De Schrijver, K., Hepatitis A-cluster in Mechelen na bezoek aan familie in Marokko. Vlaams Infectieziektenbulletin 2006. **58**(4): p. 2-9.
101. Beutels, M., et al., Prevalence of hepatitis A, B and C in the Flemish population. European Journal of Epidemiology, 1997. **13**(3): p. 275-280.
102. Quoilin, S., et al., A population-based prevalence study of hepatitis A, B and C virus using oral fluid in Flanders, Belgium. European Journal of Epidemiology, 2007. **22**(3): p. 195-202.
103. Shkedy, Z., et al., Modelling forces of infection by using monotone local polynomials. Journal of the Royal Statistical Society Series C-Applied Statistics, 2003. **52**: p. 469-485.
104. Shkedy, Z., et al., Modelling age-dependent force of infection from prevalence data using fractional polynomials. Statistics in Medicine, 2006. **25**(9): p. 1577-1591.
105. Namata, H., et al., Estimation of the force of infection from current status data using generalized linear mixed models. Journal of Applied Statistics, 2007. **34**(8): p. 923-939.
106. Hens, N., et al., Modelling multisera data: The estimation of new joint and conditional epidemiological parameters. Stat Med, 2008. **27**(14): p. 2651-64.
107. Beutels, M., et al., The shift in prevalence of hepatitis A immunity in Flanders, Belgium. Acta Gastroenterol Belg, 1998. **61**(1): p. 4-7.
108. Adam, R., et al., Evolution of liver transplantation in Europe: report of the European Liver Transplant Registry. Liver Transpl, 2003. **9**(12): p. 1231-43.
109. Karam, V., et al., Quality control of the European Liver Transplant Registry: results of audit visits to the contributing centers. Transplantation, 2003. **75**(12): p. 2167-73.
110. Algemene Directie Werkgelegenheid en Arbeidsmarkt. De immigratie in Belgie: aantallen, stromen en arbeidsmarkt. 2007: Brussels. p. 68.
111. Koning Boudewijnstichting & het Centrum voor gelijkheid van kansen en voor racismebestrijding.
Belgische debatten voor een migratiebeleid. Facts and figures. 2008: Brussels. p. 139.
112. Beutels, P., et al., Economic evaluation of vaccination programmes: a consensus statement focusing on viral hepatitis. Pharmacoeconomics, 2002. **20**(1): p. 1-7.
113. Beutels, P., et al., Methodological issues and new developments in the economic evaluation of vaccines. Expert Rev Vaccines, 2003. **2**(5): p. 649-60.
114. Brisson, M. and W.J. Edmunds, Economic evaluation of vaccination programs: the impact of herd-immunity. Med Decis Making, 2003. **23**(1): p. 76-82.
115. Valenzuela, M.T., et al., Cost-effectiveness of universal childhood hepatitis A vaccination in Chile. Vaccine, 2005. **23**(32): p. 4110-4119.
116. Armstrong, G.L., et al., The economics of routine childhood hepatitis A immunization in the United States: the impact of herd immunity. Pediatrics, 2007. **119**(1): p. e22-9.
117. Rein, D.B., et al., Cost-effectiveness of routine childhood vaccination for hepatitis A in the United States. Pediatrics, 2007. **119**(1): p. e12-21.

118. Van Effelterre, T.P., et al., A mathematical model of hepatitis a transmission in the United States indicates value of universal childhood immunization. Clin Infect Dis, 2006. **43**(2): p. 158-64.
119. Lopez, E., et al., The cost-effectiveness of universal vaccination of children against hepatitis A in Argentina: results of a dynamic health-economic analysis. J Gastroenterol, 2007. **42**(2): p. 152-60.
120. Bauch, C.T., et al., A dynamic model for assessing universal Hepatitis A vaccination in Canada. Vaccine, 2007. **25**(10): p. 1719-26.
121. Srinivasa Rao, A.S., et al., Cohort effects in dynamic models and their impact on vaccination programmes: an example from hepatitis A. BMC Infect Dis, 2006. **6**: p. 174.
122. Postma, M.J., et al., Pharmaco-economic evaluation of targeted hepatitis A vaccination for children of ethnic minorities in Amsterdam (The Netherlands). Vaccine, 2004. **22**(15-16): p. 1862-7.
123. Haight, F.A. and M.A. Breuer, The Borel-Tanner Distribution. Biometrika, 1960. **47**(1-2): p. 143-150.
124. Mossong, J., et al., Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med, 2008. **5**(3): p. e74.
125. Meltzer, M.I., et al., The economics of vaccinating restaurant workers against hepatitis A. Vaccine, 2001. **19**(15-16): p. 2138-45.
126. Howitz, M.F., et al., [The economic impact of an epidemic of hepatitis A among men who have sex with men]. Ugeskr Laeger, 2007. **169**(41): p. 3489-92.
127. Chodick, G., et al., Cost-utility analysis of hepatitis A prevention among health-care workers in Israel. J Occup Environ Med, 2002. **44**(2): p. 109-15.
128. Egoz, N., Cost-benefit of mass prophylaxis with immune serum globulin to control waterborne hepatitis A: a case study. Isr J Med Sci, 1986. **22**(3-4): p. 277-82.
129. Patnaik, J.L., L. Dippold, and R.L. Vogt, Hepatitis A in a food worker and subsequent prophylaxis of restaurant patrons. J Environ Health, 2006. **69**(1): p. 16-8, 24, 26.
130. Das, A., An economic analysis of different strategies of immunization against hepatitis A virus in developed countries. Hepatology, 1999. **29**(2): p. 548-52.
131. Szucs, T., Cost-effectiveness of hepatitis A and B vaccination programme in Germany. Vaccine, 2000. **18 Suppl 1**: p. S86-9.
132. Ellis, A., et al., Cost-effectiveness of childhood hepatitis A vaccination in Argentina: a second dose is warranted. Rev Panam Salud Publica, 2007. **21**(6): p. 345-356.
133. Navas, E., et al., Efficiency of the incorporation of the hepatitis A vaccine as a combined A+B vaccine to the hepatitis B vaccination programme of preadolescents in schools. Vaccine, 2005. **23**(17-18): p. 2185-9.
134. Krahn, M., Universal Hepatitis A Vaccination for Adolescents and Children in Canada: A cost-effectiveness analysis., in Canadian Communicable Disease Reports. 2003.
135. Arnal, J.M., et al., Cost effectiveness of hepatitis A virus immunisation in Spain. Pharmacoeconomics, 1997. **12**(3): p. 361-73.
136. Bauch, C., et al. Cost-effectiveness of universal hepatitis A in Canada. in The Canadian Immunisation Conference. 2006. Winnipeg, Manitoba, Canada.
137. Rajan, E., A.G. Shattock, and J.F. Fielding, Cost-effective analysis of hepatitis A prevention in Ireland. Am J Gastroenterol, 2000. **95**(1): p. 223-6.
138. Severo, C.A., F. Fagnani, and A. Lafuma, Cost effectiveness of hepatitis A prevention in France. Pharmacoeconomics, 1995. **8**(1): p. 46-61.
139. Van Doorslaer, E., G. Tormans, and P. Van Damme, Cost-effectiveness analysis of vaccination against hepatitis A in travellers. J Med Virol, 1994. **44**(4): p. 463-9.
140. Tormans, G., P. Van Damme, and E. Van Doorslaer, Cost-effectiveness analysis of hepatitis A prevention in travellers. Vaccine, 1992. **10 Suppl 1**: p. S88-92.
141. Jacobs, R.J., S. Saab, and A.S. Meyerhoff, The cost effectiveness of hepatitis immunization for US college students. J Am Coll Health, 2003. **51**(6): p. 227-36.

142. Jacobs, R.J., G.A. Gibson, and A.S. Meyerhoff, Cost-effectiveness of hepatitis A-B vaccine versus hepatitis B vaccine for healthcare and public safety workers in the western United States. Infection Control and Hospital Epidemiology, 2004. **25**(7): p. 563-569.

143. Buma, A.H., et al., An economic evaluation of hepatitis A vaccination in Dutch military personnel. Mil Med, 1998. **163**(8): p. 564-7.

144. Jefferson, T.O., R.H. Behrens, and V. Demicheli, Should British soldiers be vaccinated against hepatitis A? An economic analysis. Vaccine, 1994. **12**(15): p. 1379-83.

145. Jakiche, R., et al., The cost-effectiveness of two strategies for vaccinating US veterans with hepatitis C virus infection against hepatitis A and hepatitis B viruses. American Journal of the Medical Sciences, 2007. **333**(1): p. 26-34.

146. Jacobs, R.J., P. Rosenthal, and A.S. Meyerhoff, Cost effectiveness of hepatitis A/B versus hepatitis B vaccination for US prison inmates. Vaccine, 2004. **22**(9-10): p. 1241-8.

147. Jacobs, R.J., et al., Cost effectiveness of vaccinating food service workers against hepatitis A infection. J Food Prot, 2000. **63**(6): p. 768-74.

148. Jacobs, R.J. and A.S. Meyerhoff, Cost-effectiveness of hepatitis A/B vaccine versus hepatitis B vaccine in public sexually transmitted disease clinics. Sex Transm Dis, 2003. **30**(11): p. 859-65.

149. Arguedas, M.R., et al., The cost-effectiveness of hepatitis A vaccination in patients with chronic hepatitis C viral infection in the United States. Am J Gastroenterol, 2002. **97**(3): p. 721-8.

150. Jacobs, R.J., R.S. Koff, and A.S. Meyerhoff, The cost-effectiveness of vaccinating chronic hepatitis C patients against hepatitis A. Am J Gastroenterol, 2002. **97**(2): p. 427-34.

151. Teppakdee, A., et al., Cost-benefit analysis of hepatitis a vaccination in Thailand. Southeast Asian J Trop Med Public Health, 2002. **33**(1): p. 118-27.

152. Gutersohn, T., et al., Hepatitis A infection in aircrews: risk of infection and cost-benefit analysis of hepatitis A vaccination. Aviat Space Environ Med, 1996. **67**(2): p. 153-6.

153. Mann, J.M., et al., Assessment of immunoglobulin use for hepatitis A control in New Mexico. Public Health Rep, 1982. **97**(6): p. 516-20.

154. Jefferson, T., V. Demicheli, and D. Wright, An economic evaluation of the introduction of vaccination against hepatitis A in a peacekeeping operation. The case of the United Nations Protection Force in Yugoslavia. Int J Technol Assess Health Care, 1994. **10**(3): p. 490-7.

155. Gillis, D., et al., Active versus passive immunization against hepatitis A in the Israel defence forces: a cost-benefit analysis. Vaccine, 2000. **18**(26): p. 3005-10.

156. Ginsberg, G.M., P.E. Slater, and D. Shouval, Cost-benefit analysis of a nationwide infant immunization programme against hepatitis A in an area of intermediate endemicity. Journal of Hepatology, 2001. **34**(1): p. 92-99.

This page is left intentionally blank.

Wettelijk depot : D/2008/10.273/88

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase 1). D/2004/10.273/2.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
7. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
8. Financieringssystemen van ziekenhuisgeneesmiddelen: een beschrijvende studie van een aantal Europese landen en Canada. D/2004/10.273/15.
9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
15. Evolutie van de uitgaven voor gezondheidszorg. D/2005/10.273/13.
16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II : ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
17. Evaluatie van de referentiebedragen. D/2005/10.273/17.
18. Prospectief bepalen van de honoraria van ziekenhuisartsen op basis van klinische paden en guidelines: makkelijker gezegd dan gedaan.. D/2005/10.273/19.
19. Evaluatie van forfaitaire persoonlijk bijdrage op het gebruik van spoedgevallendienst. D/2005/10.273/21.
20. HTA Moleculaire Diagnostiek in België. D/2005/10.273/23, D/2005/10.273/25.
21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/29.
23. HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA). D/2005/10.273/32.
24. Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen. D/2005/10.273/34.
25. Capsule endoscopie. D/2006/10.273/01.
26. Medico–legale aspecten van klinische praktijkrichtlijnen. D2006/10.273/05.
27. De kwaliteit en de organisatie van type 2 diabeteszorg. D2006/10.273/07.
28. Voorlopige richtlijnen voor farmaco-economisch onderzoek in België. D2006/10.273/10.
29. Nationale Richtlijnen College voor Oncologie: A. algemeen kader oncologisch kwaliteitshandboek B. wetenschappelijke basis voor klinische paden voor diagnose en behandeling colorectale kanker en testiskanker. D2006/10.273/12.
30. Inventaris van databanken gezondheidszorg. D2006/10.273/14.
31. Health Technology Assessment prostate-specific-antigen (PSA) voor prostaatkankerscreening. D2006/10.273/17.
32. Feedback : onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport : deel II. D/2006/10.273/19.
33. Effecten en kosten van de vaccinatie van Belgische kinderen met geconjugeerd pneumokokkenvaccin. D/2006/10.273/21.
34. Trastuzumab bij vroegtijdige stadia van borstkanker. D/2006/10.273/23.
35. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase III)- precisering van de kostenraming. D/2006/10.273/26.
36. Farmacologische en chirurgische behandeling van obesitas. Residentiële zorg voor ernstig obese kinderen in België. D/2006/10.273/28.
37. HTA Magnetische Resonantie Beeldvorming. D/2006/10.273/32.

38. Baarmoederhalskankerscreening en testen op Human Papillomavirus (HPV). D/2006/10.273/35
39. Rapid assessment van nieuwe wervelzuil technologieën : totale discusprothese en vertebro/ballon kyfoplastie. D/2006/10.273/38.
40. Functioneel bilan van de patiënt als mogelijke basis voor nomenclatuur van kinesitherapie in België? D/2006/10.273/40.
41. Klinische kwaliteitsindicatoren. D/2006/10.273/43.
42. Studie naar praktijkverschillen bij electieve chirurgische ingrepen in België. D/2006/10.273/45.
43. Herziening bestaande praktijkrichtlijnen. D/2006/10.273/48.
44. Een procedure voor de beoordeling van nieuwe medische hulpmiddelen. D/2006/10.273/50.
45. HTA Colorectale Kankerscreening: wetenschappelijke stand van zaken en budgetimpact voor België. D/2006/10.273/53.
46. Health Technology Assessment. Polysomnografie en thuismonitoring van zuigelingen voor de preventie van wiegendood. D/2006/10.273/59.
47. Geneesmiddelengebruik in de belgische rusthuizen en rust- en verzorgingstehuizen. D/2006/10.273/61
48. Chronische lage rugpijn. D/2006/10.273/63.
49. Antivirale middelen bij seizoensgriep en grieppandemie. Literatuurstudie en ontwikkeling van praktijkrichtlijnen. D/2006/10.273/65.
50. Eigen betalingen in de Belgische gezondheidszorg. De impact van supplementen. D/2006/10.273/68.
51. Chronische zorgbehoeften bij personen met een niet- aangeboren hersenletsel (NAH) tussen 18 en 65 jaar. D/2007/10.273/01.
52. Rapid Assessment: Cardiovasculaire Primaire Preventie in de Belgische Huisartspraktijk. D/2007/10.273/03.
53. Financiering van verpleegkundige zorg in ziekenhuizen. D/2007/10 273/06
54. Kosten-effectiviteitsanalyse van rotavirus vaccinatie van zuigelingen in België
55. Evidence-based inhoud van geschreven informatie vanuit de farmaceutische industrie aan huisartsen. D/2007/10.273/12.
56. Orthopedisch Materiaal in België: Health Technology Assessment. D/2007/10.273/14.
57. Organisatie en Financiering van Musculoskeletale en Neurologische Revalidatie in België. D/2007/10.273/18.
58. De Implanteerbare Defibrillator: een Health Technology Assessment. D/2007/10.273/21.
59. Laboratoriumtesten in de huisartsgeneeskunde. D2007/10.273/24.
60. Longfunctie testen bij volwassenen. D/2007/10.273/27.
61. Vacuümgeassisteerde Wondbehandeling: een Rapid Assessment. D/2007/10.273/30
62. Intensiteitsgemoduleerde Radiotherapie (IMRT). D/2007/10.273/32.
63. Wetenschappelijke ondersteuning van het College voor Oncologie: een nationale praktijkrichtlijn voor de aanpak van borstkanker. D/2007/10.273/35.
64. HPV Vaccinatie ter Preventie van Baarmoederhalskanker in België: Health Technology Assessment. D/2007/10.273/41.
65. Organisatie en financiering van genetische diagnostiek in België. D/2007/10.273/44.
66. Health Technology Assessment: Drug-Eluting Stents in België. D/2007/10.273/47
67. Hadrontherapie. D/2007/10.273/50.
68. Vergoeding van schade als gevolg van gezondheidszorg – Fase IV : Verdeelsleutel tussen het Fonds en de verzekeraars. D/2007/10.273/52.
69. Kwaliteit van rectale kankerzorg – Fase 1: een praktijkrichtlijn voor rectale kanker D/2007/10.273/54.
70. Vergelijkende studie van ziekenhuisaccrediterings-programma's in Europa D/2008/10.273/57.
71. Aanbevelingen voor het gebruik van vijf oftalmologische testen in de klinische praktijk .D/2008/10.273/04
72. Het aanbod van artsen in België. Huidige toestand en toekomstige uitdagingen. D/2008/10.273/07
73. Financiering van het zorgprogramma voor de geriatrische patiënt in algemene ziekenhuizen: definitie en evaluatie van een geriatrische patiënt, definitie van de interne liaisongeriatrie en evaluatie van de middelen voor een goede financiering. D/2008/10.273/11
74. Hyperbare Zuurstoftherapie: Rapid Assessment. D/2008/10.273/13.
75. Wetenschappelijke ondersteuning van het College voor Oncologie: een nationale praktijkrichtlijn voor de aanpak van slokdarm- en maagkanker. D/2008/10.273/16.

76. Kwaliteitsbevordering in de huisartsenpraktijk in België: status quo of quo vadis? D/2008/10.273/18.
77. Orthodontie bij kinderen en adolescenten. D/2008/10.273/20.
78. Richtlijnen voor farmaco-economische evaluaties in België. D/2008/10.273/23.
79. Terugbetaling van radioisotopen in België. D/2008/10.273/26
80. Evaluatie van de effecten van de maximumfactuur op de consumptie en financiële toegankelijkheid van gezondheidszorg. D/2008/10.273/35.
81. Kwaliteit van rectale kankerzorg – phase 2: ontwikkeling en test van een set van kwaliteitsindicatoren. D/2008/10.273/38
82. 64-Slice computertomografie van de kransslagaders bij patiënten met vermoeden van coronaire hartziekte. D/2008/10.273/40
83. Internationale vergelijking van terugbetalingsregels en juridische aspecten van plastische heelkunde. D/200810.273/43
84. Langverblijvende psychiatrische patiënten in T-bedden. D/2008/10.273/46
85. Vergelijking van twee financieringssystemen voor de eerstelijnszorg in België. D/2008/10.273/49.
86. Functiedifferentiatie in de verpleegkundige zorg: mogelijkheden en beperkingen. D/2008/10.273/52.
87. Het gebruik van kinesitherapie en van fysische geneeskunde en revalidatie in België. D/2008/10.273/54.
88. Chronisch Vermoeidheidssyndroom: diagnose, behandeling en zorgorganisatie. D/2008/10.273/58.
89. Rapid assessment van enkele nieuwe behandelingen voor prostaatkanker en goedaardige prostaathypertrofie. D/2008/10.273/61
90. Huisartsgeneeskunde: aantrekkingskracht en beroepstrouw bevorderen. D/2008/10.273/63
91. Hoorapparaten in België: health technology assessment. D/2008/10.273/67
92. Nosocomiale infecties in België, deel 1: nationale prevalentiestudie. D/2008/10.273/70.
93. Detectie van adverse events in administratieve databanken. D/2008/10.273/73.
94. Intensieve maternele verzorging (Maternal Intensive Care) in België. D/2008/10.273/77
95. Percutane hartklep implantatie bij congenitale en degeneratieve klepletsels: A rapid Health Technology Assessment. D/2008/10.273/79
96. Het opstellen van een medische index voor private ziekteverzekerings-overeenkomsten. D/2008/10.273/82
97. NOK/PSY revalidatiecentra: doelgroepen, wetenschappelijke evidentie en zorgorganisatie. D/2009/10.273/84
98. Evaluatie van universele en doelgroep hepatitis A vaccinatie opties in België. D/2008/10.273/88