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Economic evaluation of prevention: further evidence

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Abstract

Economic evaluation of prevention: further evidence

This report is the third in a series of reports that aim to identify cost-effective preventive interventions that have not yet been diffused into the Dutch health care system or into a public health setting.

In the first part of this report, five new interventions are presented and at the same time, renew the information on cost-effectiveness and implementation issues for six interventions that were described in less detail in our first report. For all eleven interventions, brief information on the magnitude and character of the health problem is presented, along with information on the intervention, its cost-effectiveness, and issues related to the transferability of foreign study results to the Dutch situation and possible future implementation of the intervention in the Netherlands. There is strong evidence for cost-effectiveness for (1) screening for neonatal group beta streptococcal infections, (2) fluoridation of drinking water, (3) mandatory folic acid fortification of staple foods, (4) vaccination against varicella zoster virus and (5) stop smoking interventions. Evidence on cost-effectiveness is moderate for (6) influenza vaccination of healthy working adults, (7) rotavirus vaccination of newborns, (8) universal hepatitis B vaccination, (9) pertussis vaccination of adolescents, (10) human papilomavirus vaccination of adolescents, and (11) pneumococcal vaccination of elderly persons. However, for all interventions, we conclude that the transferability of the results to the Dutch situation is poor and more research is needed to investigate cost-effectiveness in the Dutch context. With respect to implementation opportunities, it is anticipated that screening for neonatal group beta streptococcal infections, pertussis vaccination of adolescents, influenza vaccination of healthy working adults and pneumococcal vaccination of elderly persons is feasible.

In the second part of this report, the cost-effectiveness was modelled for two interventions that were shown to be cost-effective in an international context and had no major barriers for implementation in the Netherlands. The two interventions were the prevention of recurrent depression by maintenance cognitive behavioural therapy (mCBT), and the prevention of chronic diseases by pharmacologic treatment of obesity. The analyses showed that mCBT is more cost-effective than usual care, which is prescription of anti-depressive medication. Compared to usual care, mCBT has a cost-effectiveness ratio of € 15,000 per QALY. The cost-effectiveness of providing pharmacologic treatment (Orlistat) in combination with a diet is relatively high. Costs per QALY gained are € 62,000 for Orlistat plus diet compared to diet alone. The modelling study underlines the importance of performing Dutch specific cost-effectiveness analyses and confirms the low transferability of foreign studies to the Dutch situation as was shown in the first part of the report.

Key words: cost-effectiveness analysis, economic evaluation, modelling, prevention, health protection, health promotion, vaccination, screening,

Rapport in het kort

Economische evaluatie van preventie: nadere bewijslast

Dit rapport is de derde in een serie van rapporten over de doelmatigheid van preventieve interventies die nog niet systematisch in Nederland in de (openbare) gezondheidzorg zijn ingevoerd.

In het eerste deel van dit rapport worden vijf nieuwe preventieve interventies gepresenteerd en wordt tevens de kennis ten aanzien van zes eerder beschreven interventies up-to-date gemaakt. Per interventie wordt achtereenvolgens het gezondheidsprobleem waar de interventie op gericht is, de interventie zelf, de doelmatigheid (kosteneffectiviteit) op basis van buitenlandse studies, de kansrijkheid van invoering en de vertaalbaarheid van de resultaten naar de Nederlandse situatie beschreven. Het onderzoek toont aan dat er sterke bewijslast voor kosteneffectiviteit is voor de volgende interventies: (1) screening op neonatale groep bèta-streptokokkeninfecties, (2) fluoridering van het drinkwater, (3) verplicht verrijken van graanproducten met foliumzuur, (4) varicella zoster (waterpokken) virusvaccinatie en (5) stoppen-met-roken interventies via de huisarts. De bewijslast voor kosteneffectiviteit is matig voor (6) griepvaccinatie bij gezonde werknemers, (7) rotavirus-vaccinatie bij pasgeborenen, (8) universele hepatitis B-vaccinatie, (9) pertussis (kinkhoest) vaccinatie bij adolescenten, (10) humane papiloma virus vaccinatie bij adolescenten en (11) pneumokokkenvaccinatie bij ouderen. Echter, bij alle interventies is de vertaalbaarheid van buitenlandse onderzoeksresultaten naar de Nederlandse situatie beperkt en is meer onderzoek nodig om de doelmatigheid in de Nederlandse context te bestuderen. Met betrekking tot de haalbaarheid van invoering wordt screening op neonatale groep bèta-streptokokken infecties, pertussis vaccinatie bij adolescenten, griepvaccinatie bij gezonde werknemers en pneumokokken vaccinatie bij ouderen kansrijk geacht.

In het tweede deel van het rapport wordt de doelmatigheid van twee interventies berekend, die in het buitenland kosteneffectief zijn gebleken en waarbij geen belangrijke barrières bij de implementatie te verwachten zijn. Dit zijn terugvalpreventie van depressie door regelmatige cognitieve gedragstherapie (mCBT) en preventie van chronische ziekten door farmacologische behandeling van obesitas. Uit de economische evaluatie bleek dat mCBT doelmatiger is dan de huidige behandeling, die bestaat uit het voorschrijven van anti-depressiva. De kosteneffectiviteitsratio van mCBT is € 15.000 per QALY. De doelmatigheid van het verstrekken van farmacologische behandeling (Orlistat) in combinatie met een dieet is relatief hoog. De kosten per gewonnen QALY zijn € 62.000 voor Orlistat in combinatie met een dieet ten opzichte van dieet alleen. De modelleerstudie onderstreept het belang van de uitvoering van economische evaluaties in de Nederlandse context en bevestigt de slechte vertaalbaarheid van buitenlandse studies naar de Nederlandse situatie.

Trefwoorden: kosteneffectiviteitsanalyse, economische evaluatie, modeleren, preventie, gezondheidsgebescherming, gezondheidsbevordering, vaccinatie, screening

Preface

This report describes the evidence on cost-effectiveness of 11 preventive interventions. This report is the third RIVM report that is aimed at the identification of preventive interventions that might be of interest for future Dutch public health policies, in a sense that it is anticipated that health benefits are achieved within a period of five years at an acceptable level of cost-effectiveness. Two previous reports identified 18 (Dirkmaat et al., 2003) and 10 (Vijgen et al., 2005) of such interventions. The two previous reports have stimulated and renewed interest in the issue of cost-effectiveness of prevention. Among others, these reports were used as input for two national meetings on the cost-effectiveness of prevention.

The current report builds on the previous two reports. We have updated the information from the 2003 report and additionally, we have added evidence on the cost-effectiveness of five preventive interventions that have not been pointed out in one of the previous reports. Relatively to the two previous reports, we focus more on issues related to the implementation of the interventions in the Netherlands. Furthermore, we have tentatively modelled the costs and effects of implementation of two preventive interventions at population level. These interventions were identified in the previous report (Vijgen et al., 2005).

For the purpose of our study, we have interviewed Dutch experts in the field of prevention. We kindly thank these experts (listed in Appendix 5) for their collaboration and for critical feed-back on draft chapters of this report. Also, Marja Westhoff, Marijke Janssens, Tonnie Bakkenist, Mirjam L'Herminez of ZonMw and Carola Schrijvers (RIVM) commented carefully on previous versions of this report. Ingeborg Bovendeur from the Center for Public Health Forecasting contributed to data gathering for part B of this report. Many colleagues from the Center for Public Health Forecasting and the Center for Prevention and Health Services Research provided with critical feed-back on drafts of this report. We thank all of the above for their contributions to our work. Finally, we would like to thank Dr Theo Vos from the University of Queensland for providing the necessary data to build the depression simulation model.

One final remark concerns the intensive cooperation with those RIVM colleagues who work on the annual report series on developments within the National Immunization Programme in the Netherlands. As a coincidental finding, 7 out of 11 promising interventions we describe in the current report appear to be vaccinations for prevention of infectious diseases. In our report, we focus on cost-effectiveness and feasibility of implementation of the vaccination, while their report focuses on all relevant developments with regard to these vaccinations. Hence, their focus is much broader. For a more complete picture of all relevant aspects of the vaccinations concerned, we refer to their report in the relevant parts of our current report.

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Samenvatting

Dit rapport is de derde in een serie van rapporten over de doelmatigheid, ofwel kosteneffectiviteit, van preventieve interventies die nog niet systematisch in Nederland in de (openbare) gezondheidzorg zijn ingevoerd.
Het doel van het onderzoek was:

- het identificeren van preventieve interventies met bewijslast voor doelmatigheid in ten minste drie kwalitatief goede economische evaluaties;
- het up-to-date maken van de bewijslast van eerder beschreven doelmatige interventies (Dirkmaat et al., 2003) op basis van striktere criteria;
- het beschrijven van de vertaalbaarheid van de resultaten naar de Nederlandse context en de kansrijkheid van landelijke invoering.
- het modelleren van de doelmatigheid van het landelijk invoeren van twee preventieve interventies die in het buitenland kosteneffectief zijn gebleken en waarbij geen grote implementatie problemen zijn te verwachten.

Dit rapport bestaat uit twee delen. In het eerste deel (Deel A) worden vijf nieuwe preventieve interventies gepresenteerd en wordt tevens de kennis ten aanzien van zes eerder beschreven interventies up-to-date gemaakt. In het tweede deel (Deel B) wordt de doelmatigheid van twee interventies berekend, die in het buitenland kosteneffectief zijn gebleken en waarbij geen belangrijke barrières bij de invoering te verwachten zijn. Deze interventies zijn terugvalpreventie van depressie door regelmatige cognitieve gedragstherapie (mCBT) en preventie van chronische ziekten door dieet en farmacologische behandeling van obesitas.

DEEL A

Doelmatige preventieve interventies
Er is sterke bewijslast voor kosteneffectiviteit op basis van buitenlandse studies voor:
(1) screening op neonatale groep bèta-streptokokkeninfecties
(2) fluoridering van het drinkwater (update 2003 rapport)
(3) verplichte verrijking van graanproducten met foliumzuur (update 2003 rapport)
(4) varicella zoster (waterpokken) virusvaccinatie (update 2003 rapport)
(5) stoppen-met-roken interventies via de huisarts (update 2003 rapport)

De bewijslast voor doelmatigheid was matig voor:
(6) griepvaccinatie bij gezonde werknemers (update 2003 rapport)
(7) rotavirusvaccinatie bij pasgeborenen
(8) universele hepatitis B-vaccinatie
(9) pertussis (kinkhoest) vaccinatie bij adolescenten
(10) humane papiloma virusvaccinatie bij adolescenten
(11) pneumokokkenvaccinatie bij ouderen (update 2003 report).

Bij alle interventies is de vertaalbaarheid van buitenlandse onderzoeksresultaten naar de Nederlandse situatie beperkt en is meer onderzoek nodig naar de doelmatigheid in de Nederlandse context. Met betrekking tot de haalbaarheid van invoering in Nederland wordt screening op neonatale groep bèta streptokokkeninfecties, pertussis vaccinatie bij adolescenten, griepvaccinatie bij gezonde werknemers en pneumokokken vaccinatie bij

ouderen kansrijk geacht. Voor alle andere interventies worden belangrijke barrières bij landelijke invoering verwacht. Hieronder wordt in het kort per interventie de doelmatigheid op basis van buitenlandse studies, de kansrijkheid voor landelijke invoering en de vertaalbaarheid van de resultaten naar de Nederlandse situatie beschreven.

Screening op neonatale groep bèta streptokokkeninfecties
Ongeveer 2 op de 1.000 pasgeborenen ontwikkelen 'early-onset group bèta streptococcal disease' (GBS). Preventie van deze ziekte begint bij het identificeren van zwangere vrouwen met een verhoogd risico om GBS over te dragen op hun kinderen. Er zijn vier verschillende strategieën: 'risk-based strategie', 'screening-based strategie', combinatie strategie en de huidige Nederlandse strategie. De huidige Nederlandse strategie om GBS-ziekte te voorkomen lijkt niet kosteneffectief. De combinatie strategie is wel kosteneffectief (< € 10.000/QALY) en een goed alternatief voor preventie van GBS in Nederland.

Rotavirusvaccinatie pasgeborenen
Rotavirussen zijn de belangrijkste oorzaak van ernstige diarree bij zuigelingen en kinderen. Verschillende economische evaluaties tonen aan dat rotavirusvaccinatie kosten-neutraal of zelfs kostenbesparend is. Hoewel de studies betrekking hebben op een oud vaccin, lijkt het erop dat de resultaten ook gelden voor de twee nieuwe vaccins (RotaRix® and RotaTeq®). Doelmatigheid van vaccinatie in Nederland is waarschijnlijk lager dan in andere landen vanwege de lagere incidentie van rotavirus, de hogere vaccinkosten en het lagere werkverzuim door ouders. Vaccinatie tegen rotavirus kan opgenomen worden in het Rijksvaccinatieprogramma, maar het is de vraag of ouders de vaccinatie nodig zullen vinden, aangezien ouders een rotavirusinfectie als een relatief onschuldige ziekte zien.

Fluoridering van het drinkwater
Fluoridering van het drinkwater in Nederland is waarschijnlijk kostenbesparend omdat de kosten van fluoridering lager zijn dan de besparingen door vermindering van caries. Echter, de kans op fluorosis is aanzienlijk. Hoewel het praktisch uitvoerbaar lijkt, is de weerstand ten aanzien van fluoridering van drinkwater zo groot dat invoering hiervan onwaarschijnlijk is.

Verplichte verrijking van graanproducten met foliumzuur
Economische evaluaties geven aan dat het verplicht invoeren van verrijking van graanproducten met foliumzuur doelmatig is met betrekking tot de preventie van neuraalbuis-defecten. Echter, er komt steeds meer bewijslast voor andere gunstige maar ook ongunstige effecten van foliumzuur. Dit is in de bestaande economische evaluaties niet meegenomen. Om uitspraken te kunnen doen over de doelmatigheid van verrijking is daarom eerst meer onderzoek nodig naar het integrale effect van foliumzuur op de gezondheid.

Varicella zostervirusvaccinatie bij kinderen
Op basis van de internationale literatuur kan worden verondersteld dat het invoeren van varicellavaccinatie in het Rijksvaccinatieprogramma kosteneffectief is vanuit het gezondheidszorgperspectief en waarschijnlijk kostenbesparend vanuit een maatschappelijk perspectief. Echter, de precieze kosteneffectiviteit hangt af van verschillende nog onzekere factoren. Te weten: de ziektelast van waterpokken in Nederland, het effect van de vaccinatie op de incidentie van waterpokken en dekking van de vaccinatie.

Stoppen-met-roken-interventies in de huisartspraktijk
Van alle leefstijlfactoren gaat roken gepaard met de hoogste ziektelast. Het verhoogt het risico op verschillende chronische ziekten zoals, longkanker en COPD. De economische

evaluatie studies laten zien dat stoppen-met-roken interventies in de huisartspraktijk ófwel door advies ófwel door advies in combinatie met nicotinepleisters kosteneffectief zijn. De bewijslast is minder sterk voor huisartsadvies in combinatie met Bupropion. Het probleem met het vertalen van de buitenlandse studies naar de Nederlandse situatie is dat het referentie-scenario bij de economische evaluaties niet overeenkomt met de huidige Nederlandse situatie. In principe zou het niet moeilijk hoeven te zijn om stoppen-met-roken in Nederland in te voeren. Echter het succes hangt af van de medewerking van de Nederlandse huisarts en natuurlijk de rokers zelf.

Griepvaccinatie bij gezonde werknemers
Hoewel er over het algemeen relatief weinig complicaties zijn als gevolg van een griepinfectie onder werknemers, kan een infectie toch leiden tot aanzienlijk werkverzuim. De meeste studies concluderen dat griepvaccinatie van werknemers kostenbesparend is vanuit het maatschappelijk perspectief. De economische baten worden bepaald door het aantal werknemers dat kiest voor vaccinatie, de mate waarin het vaccin aansluit bij de heersende stam, de virulentie van de heersende stam, de mate van werkverzuim en het productiviteitsverlies door de ziekte. In de praktijk zal het niet moeilijk zijn om vaccinatie aan de werknemers in Nederland aan te bieden. Echter, de vaccinatiegraad is sterk gerelateerd aan de perceptie van de ernst van de ziekte en gezien de griep over het algemeen niet als ernstig wordt beschouwd, kan dit een belangrijke rol spelen bij het bereik van de vaccinatie.

Universele hepatitis B-vaccinatie
Hepatitis B is een zeer besmettelijke ziekte. In Nederland komt het relatief weinig voor, maar er zijn wel een aantal hoogrisicogroepen zoals homoseksuelen, prostituees, drugsgebruikers en sommige immigranten. Vanwege de lage prevalentie heeft de Nederlandse overheid ervoor gekozen om geen universele vaccinatie uit te voeren, maar om een hoogrisicogroep benadering te kiezen. Hoewel de bewijslast voor kosteneffectiviteit van universele vaccinatie niet overtuigend is in gebieden met een lage prevalentie, zijn er wel aanwijzingen dat vaccinatie van adolescenten en vaccinatie van zuigelingen doelmatig is. De kosten-effectiviteit van universele vaccinatie hangt naar verwachting samen met de manier waarop deze vaccinatie in Nederland geïmplementeerd zou worden. Bij zuigelingen is het onwenselijk om op één prikmoment drie verschillende vaccinaties te geven. Een oplossing is om het commerciële combinatievaccin (DTP-IPV-HepB-Hib) te gebruiken. Dit wordt momenteel al gebruikt voor pasgeboren kinderen afkomstig uit risicogroepen. Vaccinatie van adolescenten vergt vergaande veranderingen in het Rijksvaccinatieprogramma (RVP) omdat een gehele nieuwe doelgroep zal moeten worden benaderd. Echter, mogelijk kan bij adolescentenvaccinatie met twee vaccinatiemomenten volstaan worden.

Pertussisvaccinatie bij adolescenten
Vaccinatie van adolescenten ter preventie van pertussis (kinkhoest) bij zuigelingen en adolescenten lijkt kosteneffectief. Echter, er zijn wel onzekerheden ten aanzien van de schatting van de incidentie van pertussis, de transmissie routes en de mate van groepsimmuniteit. De kosteneffectiviteitsratio varieert van kostenbesparend tot € 186.000 per gewonnen levensjaar afhankelijk van de veronderstelde groepsimmuniteit. Op dit moment loopt er een Nederlandse studie op dit terrein en de resultaten hiervan zullen meer inzicht in de doelmatigheid in Nederland geven. Daarnaast moet er meer inzicht komen in de incidentie van pertussis, de effectiviteit van het vaccin en negatieve bijwerkingen voordat een beslissing over invoering in Nederland genomen kan worden.

Humane papiloma virus (HPV) vaccinatie bij adolescenten
HPV vaccinatie van vrouwelijke adolescenten is waarschijnlijk kosteneffectief, hoewel de studies nog wel enige variatie laten zien. De ratio's variëren van € 12.225 tot € 24.152 per gewonnen QALY. De resultaten lijken afhankelijk te zijn van de leeftijd waarop de vaccinatie wordt gegeven, de effectiviteit van het vaccin, de prijs van het vaccin en de duur van bescherming. Er is dus meer onderzoek nodig naar de bijdrage van deze factoren als wel naar de kosteneffectiviteit van HPV-vaccinatie bij mannen. De bijdrage van de vaccinatie op de screeningsfrequentie is ook belangrijk. Universele HPV-vaccinatie bij pre-adolescente meisjes in Nederland is waarschijnlijk alleen kosteneffectief bij bepaalde 'base case' assumpties. De haalbaarheid van invoering van HPV-vaccinatie in Nederland hangt onder andere af van de vaccinprijs en de bekendheid van de ouders en adolescenten ten aanzien van het belang van vaccinatie en screening.

Pneumokokkenvaccinatie bij ouderen
Een bacteriële infectie van *Streptococcus pneumoniae* kan meningitis, bloedvergiftiging en longontsteking veroorzaken. De kosteneffectiviteit van vaccinatie varieert tussen kostenbesparend tot € 31.000 per gewonnen QALY. De vertaalbaarheid van de buitenlandse resultaten naar de Nederlandse situatie wordt bemoeilijkt door een lagere incidentie van ziekten veroorzaakt door pneumokokken en de mogelijke afhankelijkheid tussen de griepvaccinatie en de pneumokokkenvaccinatie. Invoering van pneumokokkenvaccinatie in Nederland lijkt haalbaar, maar vaccinatie tegen pneumokokken gerelateerde ziekten kan de vaccinatiegraad van griepvaccinatie mogelijk negatief beïnvloeden.

Economische evaluatie en beleidsontwikkeling
De informatie beschreven in dit rapport is bedoeld om beleidsmakers te ondersteunen bij keuzes ten aanzien van het gezondheidsbeleid. Echter, deze keuzes zijn niet alleen gebaseerd op kosteneffectiviteit, maar ook op andere factoren zoals de totale kosten van een interventie, principes van solidariteit en gelijkheid en de ernst van de ziekte, zowel op het niveau van de volksgezondheid als van het individu. Kosteneffectiviteit is weliswaar maar één aspect van het beleidsontwikkelingsproces, maar het wordt wel gezien als een belangrijk aspect.
In ons rapport zijn alleen interventies opgenomen waarvan tenminste drie goede economische evaluaties beschikbaar waren die een goede kosteneffectiviteit aantoonden (tot ± € 20.000 per QALY). Hoewel dit informatief is voor beleidsbeslissingen, gaat dit voorbij aan inzicht in preventieve interventies die niet kosteneffectief zijn. Deze kennis is ook van belang voor het beleid, omdat het de invoering van dergelijke interventies zou kunnen tegengaan, of bestaande kostenineffectieve interventies zouden kunnen worden stopgezet. Een andere beperking in deze aanpak is dat de studies wel inzicht geven in de kosteneffectiviteit, de haalbaarheid en de vertaalbaarheid van buitenlandse studies, maar er wordt geen prioritering aangegeven ten aanzien van welke interventies als eerste ingevoerd zouden moeten worden in de (openbare) gezondheidszorg.

Kosteneffectiviteit vooral bekend bij ziektepreventie
Net als in onze vorige rapporten moeten we opnieuw constateren dat de meeste kennis over kosteneffectiviteit betrekking heeft op interventies in het domein van ziektepreventie. Van de elf interventies beschreven in dit rapport zijn er acht afkomstig uit het domein van ziektepreventie (met name vaccinaties), twee uit het domein van gezondheidsbescherming en slechts één uit het domein van gezondheidsbevordering. Geen enkele had betrekking op interventies in het kader van integraal gezondheidsbeleid. Het opnemen van nieuwe vaccins in het Rijksvaccinatieprogramma is niet gemakkelijk. Naast budgetaire overwegingen en de

ziektelast moeten nog veel andere factoren onderzocht worden alvorens de nieuwe vaccins te kunnen invoeren.

DEEL B

Doorrekening van het landelijk invoeren van twee interventies
In het tweede deel van dit rapport zijn twee modelleerstudies uitgevoerd naar de kosteneffectiviteit van interventies die niet systematisch in Nederland zijn ingevoerd, maar waarvan in het buitenland wel de kosteneffectiviteit is aangetoond: preventie van terugval van depressie door regelmatige cognitieve gedragstherapie (mCBT) en de preventie van chronische ziekten door farmacologische behandeling van obesitas in combinatie met een dieet. Van deze interventies wordt verwacht dat invoering geen belangrijke barrières heeft.

Terugvalpreventie van depressie door regelmatige cognitieve gedragstherapie (mCBT)
Belangrijke gezondheidswinst kan worden bereikt tegen lage kosten als de huisarts mensen met een ernstige depressie regelmatige cognitieve gedragstherapie laat ondergaan in plaats van hen antidepressiva voor te schrijven. Zowel bij mensen die zojuist hersteld zijn van een depressieve periode, als bij een gemengde populatie (dat wil zeggen met verschillende periode sinds herstel) is de incrementele kosteneffectiviteitsratio lager dan € 20.000 per gewonnen QALY. Wanneer iemand die zojuist hersteld is van een depressieve periode mCBT krijgt in plaats van de huidige behandeling (antidepressiva) wint hij/zij gemiddeld ongeveer 0,10 QALY in een periode van vijf jaar tegen ongeveer € 500 extra kosten. Dit resulteert in een gemiddelde kosteneffectiviteitsratio van € 5.000 per gewonnen QALY. In een gemengde populatie is de gezondheidswinst gemiddeld wat minder en wint een patiënt gemiddeld 0,05 QALY in een periode van vijf jaar tegen hogere kosten. Dit resulteert in een incrementele kosteneffectiviteitsratio van € 15.000 per gewonnen QALY. Deze ratio's moeten wel met enige voorzichtigheid geïnterpreteerd worden omdat er bij de berekening een aantal aannames is gemaakt die gebaseerd zijn op internationale studies, terwijl een aantal parameters, zoals therapietrouw, eigenlijk beter gebaseerd zou kunnen zijn op Nederlandse data. Deze waren echter niet beschikbaar.

Preventie van chronische ziekten door dieet en farmacologische behandeling (Orlistat) van obesitas
De kosteneffectiviteitsratio van het voorschrijven van Orlistat in combinatie met een dieet-advies is in Nederland relatief hoog. Kosten per gewonnen QALY zijn ongeveer € 18.000 voor een dieetadvies ten opzichte van geen behandeling en € 62.000 voor een Orlistatbehandeling in combinatie met een dieetadvies ten opzichte van een dieetadvies. De kosteneffectiviteitsratio's zijn relatief hoog ten opzichte van eerdere studies. Dit komt vooral omdat in de modelleerstudie de aanname is gehanteerd dat het effect van interventies op de body mass index op de langere termijn afneemt. Er is in deze studie vanuit gegaan dat op de lange termijn slechts 20% van het gewichtsverlies gehandhaafd bleef. Als er van 100% uit was gegaan dan zouden de kosten veel lager zijn, namelijk € 8.000 per gewonnen QALY voor dieetadvies en € 24.000 per gewonnen QALY voor Orlistatbehandeling in combinatie met een dieetadvies. In eerdere studies is aangetoond dat een langere en intensieve interventie de gewichtsstijging na eerder gewichtsverlies kan tegengaan. Echter, deze extra inspanningen betekenen wel weer hogere kosten en het is moeilijk om te voorspellen op welke manier dit de kosteneffectiviteit zal beïnvloeden.

De modelleerstudies onderschrijven het belang van het uitvoeren van economische evaluaties in de Nederlandse context en bevestigen de slechte vertaalbaarheid van buitenlandse studies naar de Nederlandse situatie, zoals genoemd in het eerste deel van dit rapport.

Summary

This report is the third in a series of reports that aim to identify cost-effective preventive interventions that have not yet been diffused into the Dutch health care system or into a public health setting.
The aim of the research was:

- to identify further preventive interventions with evidence on cost-effectiveness from at least three good quality economic evaluations;
- to make an update on the interventions that were previously described (Dirkmaat et al., 2003) using the more strict criteria on evidence;
- to describe the transferability of the results to the Dutch situation and implementation issues.
- to model the cost-effectiveness of nation-wide implementation in the Netherlands of two interventions with a good cost-effectiveness profile that also appear to be without major implementation problems.

This report contains two parts. In the first part (Part A) five new interventions are presented and renew the information on cost-effectiveness and implementation issues of six interventions that were described in less detail in the first report. In the second part (Part B) the cost-effectiveness of two interventions are modelled assuming they will be implemented in the Netherlands. These interventions are: the prevention of recurrent depression by maintenance cognitive behavioural therapy, and the prevention of chronic diseases by pharmacologic treatment of obesity. These interventions were assumed not to have major barriers for implementation, and their cost-effectiveness has not yet been modelled in the Netherlands.

PART A

Cost-effective preventive interventions
There is strong evidence for cost-effectiveness based on internationally literature for:
(1) screening for neonatal group beta streptococcal infections
(2) fluoridation of drinking water (update previous report)
(3) mandatory folic acid fortification of staple foods (update previous report)
(4) vaccination against varicella zoster virus (update previous report)
(5) stop smoking interventions (update previous report)
(6) influenza vaccination of healthy working adults (update previous report)

Evidence for cost-effectiveness is moderate for:
(7) rotavirus vaccination of newborns
(8) universal hepatitis B vaccination
(9) pertussis vaccination of adolescents
(10) human papilomavirus vaccination of adolescents
(11) pneumococcal vaccination of elderly persons (update previous report).

For all interventions it is concluded that the transferability of the results to the Dutch situation is poor and more research is needed to investigate cost-effectiveness in the Dutch context. With respect to implementation opportunities, it is anticipated that screening for neonatal

group beta streptococcal infections, pertussis vaccination of adolescents, stop smoking interventions, influenza vaccination of healthy working adults and pneumococcal vaccination of elderly persons is feasible. For the other interventions some or major implementation barriers are described.
Below the cost-effectiveness of the 11 interventions is summarized.

Screening for neonatal group beta streptococcal infections
About 2 in 1,000 newborns develop early-onset group beta streptococcal disease (GBS). Prevention of this disease starts with identifying pregnant women at risk of transmitting GBS to their offspring. Four different strategies for this selection were proposed: risk-based strategy, screening-based strategy, combination strategy, and the Dutch strategy. The current Dutch strategy in the prevention of GBS disease seems to be not cost-effective. The combination strategy seems the most cost-effective (< € 10,000/QALY) and feasible method to implement as prevention strategy for GBS in the Netherlands.

Rotavirus vaccination of newborns
Rotaviruses are the most common cause of severe watery diarrheal disease in infants and young children. Several economic evaluations conclude that rotavirus vaccination would be cost-neutral or even cost-saving. Although these results are based on data on the former vaccine Rotashield®, the results are expected to be generally applicable to two new vaccines that recently became available (RotaRix® and RotaTeq®). Cost-effectiveness of vaccination is probably lower in the Netherlands because the incidence of rotavirus is lower, vaccine costs are higher and work absence of parents is less than assumed in foreign studies. Mass rotavirus vaccination could be relatively easy implemented in the Netherlands, but it remains questionable whether this vaccine is acceptable to parents who perceive a rotavirus infection to be a relatively innocent disease.

Fluoridation of drinking water
Fluoridation of drinking water in the Netherlands would probably be cost-saving as the costs of fluoridation will be outweighed by the savings due to reduction of caries. However, people would also run the risk of fluorosis. Although practically feasible, the many objections against fluoridation of drinking water make its implementation rather improbable.

Mandatory folic acid fortification of staple foods
Economic evaluations in the literature suggest that mandatory folic acid fortification of staple foods in the Netherlands is probably cost-saving with regard to the prevention of NTDs. However, recent evidence on other favourable and harmful effects of folic acid was not included in the economic evaluations. Further research is needed to gain more insight into the diverse effects of folic acid. Such a risk-benefit analysis should be the basis of future comprehensive economic evaluations of mandatory folic acid fortification and supplementation.

Vaccination against varicella zoster virus
Based on international literature it is expected that the introduction of varicella vaccination in the Dutch National Immunization Programme (NIP) could be cost-effective from a healthcare payer perspective and possibly even cost-saving from a societal perspective. Nevertheless, the actual cost-effectiveness depends on several aspects that are still uncertain at the moment. These factors include the actual burden of disease caused by chickenpox in the Netherlands, and the effect of varicella vaccination on zoster incidence, and on MMR coverage.

Stop smoking interventions
In the Netherlands, smoking is the risk factor that is associated with the highest burden of disease. Smoking increases the risk of many diseases, such as lung cancer and COPD. The examined studies conclude that smoking cessation interventions, either GP counselling alone, or GP counselling in combination with nicotine replacement therapy would be cost-effective. Less evidence was found for GP counselling in combination with Bupropion. A concern with respect to the transferability of the results from foreign studies to the Dutch situation is that the reference scenarios do not exactly reflect the Dutch situation. Implementation of GP counselling aiming at smoking cessation in the Netherlands will not be difficult. However, the effectiveness depends to a large extent on the efforts of GPs and on compliance of smokers.

Influenza vaccination of healthy working adults
Although complications of influenza infections are uncommon among healthy working adults, infections result in significant burden of illness, especially in terms of absenteeism from work. Most studies conclude that vaccination will lead to cost-savings when the societal perspective is chosen. Economic benefits highly depend on the number of workers that choose for vaccination, the actual match for the season, the virulence of the circulating strains, and the degree of absenteeism and productivity losses due to influenza infections. In practice, it will not be difficult to offer vaccination to healthy working adults in the Netherlands. However, vaccination coverage is always strongly associated with perceptions of the severity of disease, and since influenza is in general not perceived to be a serious health threat, one can expect that this will also be the case for influenza vaccination.

Universal hepatitis B vaccination
Hepatitis B is a contagious viral infection. In the Netherlands the prevalence of hepatitis B is generally low, but higher among some risk groups (homosexuals, prostitutes, drug users) and some immigrant groups. Because of the very low endemicity, the Dutch government decided not to implement universal vaccination, but to implement risk-based prevention policies, including vaccination of risk-groups. Evidence is inconclusive on cost-effectiveness of preventive policies in low-endemic areas, but it seems that vaccination of adolescents and the vaccination of infants are both cost-effective. However, it seems that the cost-effectiveness of universal hepatitis B vaccination is related to the way it possibly will be implemented. Because it is undesirable to give more than two different vaccinations at one moment, it will be necessary to use the commercially available combination (DTP-IPV-HepB-Hib) vaccine for newborns, as currently implemented for those newborns who are at risk for hepatitis B infection. Universal vaccination of adolescents would require the introduction of an entirely different age group within the NIP.

Pertussis vaccination of adolescents
Pertussis vaccination of adolescents - aiming to prevent pertussis in both infants and adolescents - appears to be cost-effective. However, there are uncertainties in the estimates of the true incidence of pertussis morbidity, transmission routes and the extent of herd immunity. The cost-effectiveness ratios range from cost-saving to € 186,000 per life year gained depending on the level of herd immunity assumed. An ongoing study investigating the cost-effectiveness in the Netherlands will result in more conclusive information. Additional information about disease incidence, vaccine efficacy, and vaccine adverse events would contribute to a future policy decision about implementation of this vaccine.

Human papilomavirus vaccination of adolescents
HPV vaccination of female pre-adolescents is possibly cost-effective, although not all interventions as found in the studies appeared to be cost-effective. The cost-effectiveness ratios of the interventions that were cost-effective range from € 12,225 to € 24,152 per QALY gained. Nearly all the existing cost-effectiveness results appeared to be sensitive to the age at which vaccination is given, vaccine efficacy, vaccine price and duration of protection. More research is needed on those factors, as well as on the cost-effectiveness of HPV vaccination in men. The impact of the vaccination on the frequency of screening is important. Based on currently available (international) data it can be concluded that universal HPV vaccination of pre-adolescent girls in the Netherlands will only be cost-effective under certain base case assumptions. The feasibility of implementation of HPV vaccination in the Netherlands depends among others on the price of the vaccine and the knowledge of parents and adolescents about the importance of vaccination and screening. Furthermore, it is important to find the best way of providing the vaccine to adolescents in optimalizing the compliance among them.

Pneumococcal vaccination of elderly persons
A bacterial infection with Streptococcus pneumoniae causes noninvasive infections and invasive diseases such as meningitis, septicaemia and pneumonia, generally associated with bacteremia. Cost-effectiveness of vaccination varies from cost-saving to € 31,000 per QALY. Cost-effectiveness rates improve with higher age of the target group. There are several threats to the transferability of foreign study results to the Dutch situation: a lower incidence of invasive diseases caused by pneumococci and the feasible interdependency between influenza vaccination and pneumococcal vaccination. It will not be difficult to implement pneumococcal vaccination in the Netherlands. However, it may be that vaccination against pneumococcal disease influences the influenza vaccination coverage degree.

Economic evaluation and policy making
The information presented in the report is meant to support future decision making on the implementation of the interventions. However, such decision making is not only based on the cost-effectiveness but also on other aspects. These aspects include e.g. total budget impact of the intervention, equity considerations and disease impact, both at the national level (DALY loss associated with the disease) and at individual level. Hence, cost-effectiveness is only one element in the decision making process, but not an unimportant one. In the study only interventions were listed that have at least three good quality economic evaluations showing cost-effectiveness (defined as cost per QALY of maximal € 20,000). Although this is informative with regard to future decision making on the nation-wide implementation of one or more of these interventions, this focus on cost-effective interventions results in more or less ignoring the knowledge of which interventions are less cost-effective or even cost-ineffective. Such knowledge could also be informative for health policy makers, either because it makes clear that some interventions should not be introduced or that existing interventions should become redundant. Furthermore, the reports, so far, have gained insight into cost-effectiveness, transferability and implementation aspects of interventions, but there is no priority with respect to importance of implementation in the Dutch healthcare or public health system. This information would be helpful for policy makers.

Cost-effectiveness primarily known in the area of disease prevention
As in previous reports, *disease prevention* is the area that was evaluated best with regard to its cost-effectiveness. Out of the eleven interventions described in detail in this report, eight interventions are from the disease prevention area (mainly vaccinations), two from the health

protection area (fluoridation of drinking water and folic acid fortification of staple foods) and one stems from the health promotion area (stop smoking interventions). No single intervention was identified from the 'intersectoral policy' area. A decision to implement new vaccines in the National Immunization Programme is a complicated one. Besides the considerations that are key in any implementation decision on preventive interventions, such as budgetary consequences and disease impact, some very specific questions have to be answered satisfactorily before new vaccines can be introduced in the Netherlands.

PART B

Modelling effect of two interventions
In part B of this report the cost-effectiveness was modelled for prevention of recurrent depression by maintenance cognitive behavioural therapy (mCBT), and the prevention of chronic diseases by pharmacologic treatment of obesity. These interventions were assumed not to have major barriers for implementation, and their cost-effectiveness was proved internationally but not nationally.

Maintenance cognitive behavioural therapy (mCBT)
The main conclusion of the cost-effectiveness study of mCBT was that health gains can be achieved at a low cost if the GP refers persons diagnosed with major depression to mCBT instead of prescribing anti-depressive medication. Both in a cohort of people just recovered from a depressive episode and in a mixed population (with different periods since recovery) ICER fall below the threshold of € 20,000 per QALY gained. Someone who has just recovered from a depressive episode receives mCBT instead of usual care he/she gains on average about 0.10 QALY over a period of five years with at an additional cost of about € 500 resulting in an average cost-effectiveness ratio of € 5,000 per QALY gained. In the mixed population the health gains are somewhat lower and a patient on average gains 0.05 QALY over a period of five years at higher costs resulting in a mean ICER of € 15,000 per QALY gained. This conclusion should be however be interpreted with caution, since a lot of parameters in the model are based on international studies while some important model parameters, like adherence to treatments, should be preferably be based on Dutch data and, as in any modelling study, some simplifying assumptions were made.

Orlistat in combination with diet
The cost-effectiveness ratio of providing Orlistat in combination with a diet is relatively high, eventhough diet alone results in less health gain. Costs per QALY gained are € 18,000 for diet compared to no care and € 62,000 of diet plus Orlistat compared to diet. Compared to previous studies, the modelling exercise reveals a higher cost-effectiveness ratio for the treatment of obesity through a diet in combination with Orlistat. This is partly due to the assumption used in this model about the effectiveness on interventions on BMI in the long term. In this study it was assumed that 20% of the weight loss was maintained in the long run. If this relapse was not taken into account, costs would be substantially lower: € 8,000 per QALY gained for diet only and € 24,000 per QALY gained for diet in combination with Orlistat . It was shown that longer and active follow up can prevent weight regain. However, this would involve additional costs and thus it is difficult to hypothesize to what extent this would influence cost-effectiveness.

The modelling studies underline the importance of performing Dutch specific cost-effectiveness analyses and confirm the low transferability of foreign studies to the Dutch situation as was shown in the first part of the study.

Part A: Identification of cost-effective preventive interventions

1. Introduction

1.1 The cost-effectiveness of prevention

Decision makers at multiple levels need information on the evidence base of prevention. Such information should assist in decision making on implementation of and prioritization between the possible candidate interventions for public health funding or for reimbursement through health care insurance. Evidence may concern effectiveness or cost-effectiveness of the intervention, but also related subjects such as impact on the total health care budget and the burden of disease. Although many (existing) preventive interventions have at present not yet been evaluated for effectiveness and cost-effectiveness (De Wit and Brouwer, 2004), the evidence base is growing in recent years. Following developments in evidence-base medicine, a similar movement towards the practice of evidence-based public health has emerged recently (Maibach et al., 2006). Internationally, this is reflected in the publication of guidelines (Guide to community preventive services, 2006; US Preventive Services Task Force, 1996) comprehensive research reports (Goldsmith et al., 2004) and systematic reviews of the literature, including meta-analyses (published, among others, in the Cochrane database and NHS-Economic Evaluation Database).

In the Netherlands, both the Health Council (Gezondheidsraad) and the Council for Public Health and Health Care (Raad voor de Volksgezondheid en Zorg) have stated that cost-effectiveness and disease burden should play a role in decision making on reimbursement of health care (Gezondheidsraad, 2003; Raad voor de Volksgezondheid en Zorg, 2006). The most prominent example of actual use of economic evaluations in health care decision making can be found in the selective reimbursement of new pharmaceuticals. Within the field of prevention, examples of the use of economic evidence for instance can be found at the introduction of expensive national public health programmes, such as cancer screening programmes and new vaccines within the National Immunization Programme. At the same time, many preventive programmes are introduced that lack evidence on their effectiveness and cost-effectiveness. This is especially true for health promotion programmes, for health protection, for healthy public policies (health in all policies) and for local preventive programmes (Goldsmith et al., 2004; Vijgen et al., 2005; De Wit and Schuit, 2006).

While acknowledging that many preventive interventions at presence have not been evaluated with regard to effects and costs, it remains important to identify those preventive programmes that are worthwile investments, in a sense that they produce health benefits at acceptable societal costs. Therefore, the Ministry of Health, Welfare and Sports has commissioned RIVM research to identify cost-effective preventive interventions that are not yet introduced systematically within the Netherlands. This report reflects the results of this research project.

1.2 RIVM work preceding this report

From the fact that this report is subtitled ’Further evidence on the cost-effectiveness of prevention’, it can be learned that this is not the first report on this issue. Indeed, two previous reports were published, one in 2003 (Dirkmaat et al.,) and one in 2005 (Vijgen et

al.). The two previous reports and the current report all focus on cost-effectiveness of preventive interventions (defined as disease prevention, health promotion, health protection and health in all policy / healthy public policies) but differ in their specific focus. Here, these differences will be explained in some detail.

The main focus of the 2003 report was to demonstrate the fact that many preventive interventions are cost-saving or very cost-effective. The aim of the report was merely to provide with examples of cost-effective interventions, rather than to demonstrate a sound evidence base for cost-effectiveness of prevention. With € 2500 per life year / quality adjusted life year gained, a very strict threshold value for cost-effectiveness was used in this report. Preventive interventions were identified using interviews with prevention experts and literature study. Overall, 18 examples of preventive interventions were presented. Compared to the later work, relatively few restrictions were set on the evidence base for cost-effectiveness: interventions were included in the report even when only one study supported the cost-effectiveness of the intervention. From the 18 examples of cost-effective prevention mentioned in the Dirkmaat report, 14 were not yet introduced systematically (identified as unrestricted access to the intervention for all members of the group at which the intervention is targeted) in the Netherlands, implying that there was ample room for introduction of cost-saving or very cost-effective preventive interventions.

Based on this 2003 study, the Ministry of Health, Welfare and Sports asked the RIVM to continue the search for cost-effective prevention programmes in collaboration with ZonMw, the Netherlands Organisation for Health Research and Development. The 2005 report of Vijgen et al. (2005) was based on a more systematic approach to identify cost-effective interventions. Besides, more strict criteria to demonstrate cost-effectiveness were used, in comparison with the first report. Here, the explicit aim of the study was to identify preventive interventions that were not yet implemented in a systematic and continuous way in the Netherlands. The Ministry of Health, Welfare and Sports explicitly asked to identify cost-effective prevention programmes with a short term effectiveness (within five years). Evidence of cost-effectiveness was considered to be sufficient if at least three studies showed a cost-effectiveness ratio below € 20,000 per QALY, in the absence of studies showing ratios far above that cut-off point. Apart from the cost-effectiveness, also implementation aspects of these programmes in the Netherlands were investigated by expert interviews and briefly discussed. Possible interventions were identified through a top-down literature search, while economic evaluations for those preventive interventions were identified using a bottom-up search strategy. Overall, 20 preventive interventions were identified. Only those interventions that were being shown in at least three good quality economic evaluation studies to be cost-effective (defined here as a cost per life year gained / per quality adjusted life year gained below € 20,000) were selected. Finally, ten preventive interventions were selected and presented in the report.

Besides the two previous research reports, RIVM and ZonMw organized two workshops at the Ministry of Health, Welfare and Sports in 2004 and 2005. The main aim of these workshops was to inform policy makers of the Ministry of Health, Welfare and Sports on the availability of cost-effective preventive interventions, and to demonstrate the importance of prevention in general. In these workshops, further examples of cost-effective interventions were presented by RIVM and ZonMw. For the 2004 workshop, no restrictions on the amount and quality of studies supporting the cost-effectiveness were used. For the 2005 workshop, similar criteria to those used for the report of Vijgen et al. (2005) were used. A total number

of seven cost-effective preventive interventions were presented in the two workshops. The combined results of our previous work are presented in Table 1.1.

Table 1.1: Cost-effective [a] [b] preventive interventions that have not yet been implemented nationally / systematically / continuously in the Netherlands, 2005

Type of prevention	**Name of intervention**
Disease prevention	
Vaccination	Vaccination against varicella zoster virus
	Pneumococcal vaccination of elderly persons
	Influenza vaccination of healthy working adults
	Hepatitis A of selected groups of healthy adult workers
Screening	Chlamydia screening
	Colon cancer screening
	Screening for abdominal aorta aneurysm
	Screening for retinopathy in type 2 diabetes patients
	Screening for human papiloma virus combined with cervical cytology
Other disease prevention	Prevention of chronic diseases through obesitas treatment / medication
	Prevention of recurrent myocard infarct through heart revalidation
	Prevention of recurrent depression through treatment
	Prevention of sudden cardiac death through automated external defibrillators
	Prevention of hip fractures through external hipprotectors
Health protection	Fluoridation of drinking water
	Mandatory folic acid fortification of staple foods
	Prevention of head injuries through bicycle helmets in children
Health promotion	Smoking cessation programmes via general practioners
	Lifestyle programmes for type 2 diabetes patients
	Promotion of breast feeding
	Prevention of chronic back pain through back-schools
	Reduction of fat consumption to reduce heart diseases and vascular diseases
	Prevention of accidental falls in elderly persons

[a] using a threshold value of € 20,000 per life year gained / quality adjusted life year gained

[b] note that the evidence base supporting the cost-effectiveness is not comparable for all interventions

From Table 1.1 it can be seen that in three consecutive reports, a total number of 23 different interventions were identified as cost-effective, without having been implemented systematically and/or nationally in the Netherlands. Please note that the interventions as presented in Vijgen et al. (2005) were selected using much more restricted criteria than the 18 interventions that were presented in Dirkmaat et al. (2003). The majority of these 23 interventions are disease prevention interventions. No single intervention from the healthy public policies domain was identified.

1.3 Aim of the research presented in this report

The present report is built on our previous work and extended with two cost-effectiveness estimates from own modelling work. The aim of the research is:

- to identify further preventive interventions with evidence on cost-effectiveness from at least three good quality economic evaluations;
- to make an update on the interventions that were described in the Dirkmaat report (2003), using the more strict criteria on evidence (based on three or more rather than one economic evaluation);
- to pay more attention to implementation issues in comparison to the two previous reports. Promising interventions should not only be relatively cost-effective but there also should not be major barriers for implementation in the Netherlands; and finally
- to model the cost-effectiveness of nation-wide implementation in the Netherlands of two interventions with a good cost-effectiveness profile that also appear to be without major implementation problems.

1.4 Outline of this report

This report consists of two major parts, part A and part B. The two parts can be read independently. Part A describes the results of the research to identify cost-effective preventive interventions, part B presents the results of the modelling work. In chapter 2, the methodology for part A is explained. Here, all terminology that is used throughout this report is explained, including methods for economic evaluation research. In chapter 3, five new preventive interventions are presented. For each intervention the health problem, the nature of the intervention, the evidence for its cost-effectiveness, the transferability of foreign study results to the Dutch situation and implementation issues surrounding the future implementation in the Netherlands are described. Chapter 4 presents an update of preventive interventions that were first presented in the 2003 Dirkmaat report. Here, the current, more restricted, inclusion criteria are used to find out whether there is more evidence supporting the cost-effectiveness of interventions that were first presented in the Dirkmaat report. Also, these interventions are reported using the same format as used for the five new interventions that were presented in chapter 3. In chapter 5, the main findings from part A of this report are summarized and discussed.

Part B of the report is concerned with the modelling of costs and effects of widespread introduction of two preventive interventions in the Netherlands. The interventions are the prevention of recurrent depression episodes and medication to reduce weight in obese persons. Per intervention, chapter 6 describes which methods are used to model the costs and effects of widespread implementation. Furthermore, results of the models are explained.

Finally, the results of the modelling work are summarized and discussed in chapter 7 (recurrent depression) and 8 (obesity). A final discussion on part B of the report follows in chapter 9.

2. Methodology

2.1 Synopsis of economic evaluation methodology and definitions

2.1.1 Prevention

Prevention can be classified in four aproaches: disease prevention, health promotion, health protection, and health in all policy (Goldsmith et al., 2004; Vijgen et al., 2005).

Disease prevention interventions are often one-on-one activities aimed at prevention of a certain disease or detect a disease in an early stage. Disease prevention includes also activities to prevent further deterioration of disease in patients already known to have a disease. Disease prevention activities may be targeted at particular individuals (e.g., persons at high risk) or at all individuals presenting for clinical care. Examples of disease prevention are screening, vaccination programmes and providing prophylaxis.

Health promotion interventions encourage individual behaviours believed to produce positive health effects and discourage behaviours that produce negative health effects. Health promotion interventions frequently take the form of public information campaigns. While the decision to undertake the health action is ultimately up to the individual, delivery of health promotion programmes is targeted at a group or population. A media-based, lifestyle campaign is an example of a health promotion intervention.

Health protection interventions reduce health risks by changing the physical or social environment in which people live. The role of individual beneficiaries of health protection interventions is either passive or limited to compliance with laws or regulations. Health protection interventions are delivered at the organizational (e.g., hospital policy), local, provincial, national or international level. Prohibiting smoking in public places and water fluoridation are examples of a health protection intervention.

Health in all policy or healthy public policy describes social or economic interventions that affect health but do not have health as the main policy objective. The determinants of health literature provides examples of policy interventions and social programmes that have important ancillary health effects, such as restricting the placement of video gambling terminals, supportive housing, early childhood education, and the provision of income support.

2.1.2 Economic evaluation methods

A full economic evaluation compares two or more interventions (programmes) in terms of their benefits and costs. An economic evaluation consists of one of the following three approaches: cost-effectiveness analysis, cost-utility analysis, or cost-benefit analysis. All three methods measure costs in the same way; the distinguishing feature of each is the way in which benefits are measured. These different ways of measuring benefits bring with them strengths and weaknesses. The methods for assessing benefits are as follows (Drummond et al., 1997, Goldsmith et al., 2004).

Cost-effectiveness analysis (CEA)
This analysis measures the benefits of an intervention in the most appropriate natural effects or physical units, such as 'years of life gained' or 'cases prevented'. Hence, study results are expressed in terms of the additional cost of achieving another unit of the benefit (e.g., the extra cost of preventing an additional case of a condition). The intervention with the lowest cost per additional outcome is the most efficient intervention. Main advantage of cost-effectiveness analysis is that measuring benefits in natural units simplifies the analysis and is often more intuitive for users of the study. Disadvantages are reduced comparability of efficiency assessments across interventions that produce different outcomes (e.g., flu vaccination versus water fluoridation) and the need to focus on a single outcome of an intervention even when an intervention generates a number of distinct benefits.

Cost-utility analysis (CUA)
This method measures benefits in a common unit that strives to include both the quantity and quality of effects associated with an intervention, usually measured by the quality-adjusted life-year (QALY). Hence, a QALY is a measure which tries to combine a quantitative measure (years gained, et cetera) with a measure of effects of the intervention on quality of life. The most efficient intervention is the one that has the lowest cost per additional QALY generated. Measuring outcomes in a common metric such as QALYs in cost-utility analysis greatly enhances the comparability of results across different types of interventions, including those that primarily affect quality of life as well as those that have a larger impact on the number of life years gained. Cost-utility analysis is therefore a broader form of analysis than cost-effectiveness analysis, but is a variant of that approach. Compared to CEA, a key disadvantage is the considerable increase in the complexity of outcomes assessment. Some authors (Gold et al., 1996) prefer not to make a distinction between CEA and CUA, since they are very similar.

Cost-benefit analysis (CBA)
This method measures all benefits in monetary terms, so that the results are usually reported in terms of the net benefit of an intervention (benefits minus costs) or the ratio of benefits to costs. Therefore, potentially this is the broadest form of analysis, where one can ascertain whether the beneficial consequences of an intervention programme justify the costs. Cost-benefit analysis can incorporate the widest range of effects across the widest range of interventions and programmes (both inside and outside the health sector), but is often controversial because it requires that the value of the benefits, including death and disease, be expressed in monetary terms.

Perspectives
One of the first steps in an economic evaluation is to define the perspective from which an economic evaluation is conducted. The perspective refers to the point of view from which costs and effects are included and how they are valued. Examples of perspectives are the patient's, societal or health care perspective. For instance, patient travel costs count as a cost from the patient's and societal perspective, while they may not be counted from the health care perspective. In other words, an economic evaluation conducted from the societal perspective or patient perspective will be more cost-effective or cost-saving than when it is viewed from the health care perspective (Van Baal et al., 2005).

2.1.3 Generalizability of economic evaluations

An issue that can affect generalizability is the fact that many economic evaluations are context-specific and that they cannot be used in other populations. This does not invalidate the use of economic evaluation evidence as an important component of health care decision making, but necessitates a warning against simplistic approaches, as for instance, by construction of league tables which purport to provide a ranking of a wide variety of health care programmes according to their efficiency. The appropriate use of economic evaluation evidence requires detailed consideration of the quality of the evidence along with thoughtful assessment of threats to transferability to one's own setting and even, in some cases, recalibration of study results to fit better in the specific context of application (e.g., recalculate the cost-effectiveness substituting prices relevant to one's own setting for those from the study setting) (Goldsmith et al., 2004; Tan Torres Edejer et al., 2004). The difficulties of generalizing context-specific CEA studies were institutionalized by the proliferation of multiple national and subnational guidelines for CEA practice, all using slightly different methods. International guidelines have not to date been developed (Tan Torres Edejer et al., 2004). However, checklists for the transferability of foreign study results to another country were developed (Welte et al., 2004).

2.2 Methodology of the present study

2.2.1 Use of thresholds for cost-effectiveness

The term cost-effectiveness suggests that there are clear cut-off points. However, in practice there is some debate on the definition of cost-effectiveness. Recently the Council for Public Health and Health Care (RVZ) has argued that medical treatment should be reimbursed if both the disease burden is significant and the cost-effectiveness ratio is acceptable (Raad voor de Volksgezondheid en Zorg, 2006). In their advice, a threshold value for cost-effectiveness of € 80,000 per quality adjusted life year (QALY) was proposed. This threshold includes all forms of prevention and care, including life-saving treatments such as end-stage renal disease treatment, transplantations and other expensive treatments, such as cancer therapy. In our research project, we used the arbitrary cut-off point of € 20,000 per QALY. This was based on the request of the Dutch Ministry of Health, Welfare and Sport, but follows a threshold for prevention that is often used in the Netherlands. However, in health care, particularly with life-saving care, a higher cut-off point appears to be acceptable. The recent RVZ report proposed for the first time an actual threshold for medical care. In the report, the cut-off point is used as a reference and not as a hard cut-off point, because generally results are described in ranges and not as a single estimate. Also, recently it became usance to report cost-effectiveness in terms of the probability that the cost-effectiveness ratio remains below a certain threshold value for cost-effectiveness.

2.2.2 Identification of interesting interventions

To identify effective and possibly cost-effective prevention programmes three different steps were taken:

1. Experts in the field of prevention were interviewed. This interview was based on a structured questionnaire (Appendix 1). The experts were asked if they knew cost-effective prevention programmes in their specific area of expertise. These could both be published studies and ongoing studies. Based on the interviews, a total of 35 prevention programmes were identified that are potentially cost-effective (see Appendix 2).

2. On the basis of a report from the Canadian Commission investigating cost-effective prevention programmes (Goldsmith et al., 2004), 32 interventions were selected that are not yet systematically implemented in the Netherlands (see Appendix 2).
3. From the intervention programmes identified by Dirkmaat et al. (2003), ten interventions are included for re-examination. Only those interventions that are not yet systematically implemented in the Netherlands are re-examined (see Appendix 2 for details). The re-examination was done to assess these interventions using the same methodology as used for interventions described in the report of Vijgen et al. (2005) and in the current report.

2.2.3 Global screening of literature: creating a longlist

A total number of 75 prevention programmes were identified by the interviews and both reports, these interventions were globally screened on the availability of three or more good quality studies. This global screening of the literature was performed in Medline database (WinSpirs) with the basic keyword (Costs-and-cost-analysis) in MESH (Medical Subject Headings) from January 1989-April 2006. A detailed description of keywords used for the literature search can be found in Appendix 4. An additional search was performed in NHS Economic Evaluation Database (EED). Furthermore, a literature search was performed in the databases of Embase, SciSearch, Social SciSearch, Psychinfo and HECLINET by a librarian at the RIVM. This search did not identify any new economic evaluations that had not already been found during the first literature search. Studies before 1989 were excluded because it was anticipated that their results would not be accurate enough and thus, difficult to translate to the current situation. Only Dutch and English language papers were included, describing studies that are performed in developed countries.

2.2.4 From long list to short list

Based on the global screening, many interventions had to be excluded because of a lack of at least three good quality economic evaluations or because too many different operationalizations of a preventive programme were found (see Appendix 2). The quality of the studies was assessed by extracting the essential elements (e.g. perspective, reference scenario, discounting, and sensitivity analysis) of every study into a database, and judging these elements on established quality criteria (based on Drummond and Jefferson, 1996). The following preventive programmes had at least three economic evaluations of sufficient quality:

- Influenza vaccination of healthy working adults
- Fluoridation of drinking water
- Mandatory folic acid fortification of staple foods
- Vaccination against varicella zoster virus
- Stop smoking interventions
- Pneumococcal vaccination of elderly persons
- Universal hepatitis B vaccination
- Screening for neonatal group beta streptococcal infections
- Rotavirus vaccination of newborns
- Human papilloma virus vaccination of adolescents
- Pertussis vaccination of adolescents

Of all these 11 interventions, the effectiveness and cost-effectiveness was carefully reviewed. In addition, the intervention itself was described as well as the public health problem the

intervention is aimed at. In order to assess the feasibility of implementation of the interventions in the Netherlands and to assess the possibility of transfer of the published results to the Dutch situation, experts were interviewed. This is described in more detail below.

2.2.5 Criteria used for cost-effectiveness

A classification system of strong and moderate evidence was used. The qualification of strong evidence (**) was used when the evidence unequivocally pointed in the direction of cost-effectiveness (see below for criteria used), while the qualification of moderate evidence (*) was used when not all available studies support the cost-effectiveness of the intervention. The following criteria for cost-effectiveness were used

- *for cost-effectiveness studies or cost-utility studies* (those studies reporting cost-effectiveness in terms of cost per life year gained / cost per quality adjusted life year gained): The qualification of strong evidence (**) was given when three or more studies show cost-effectiveness not exceeding € 20.000 per life year gained (LYG) or per quality adjusted life year gained (QALY) while the ranges around the point estimates do not exceed € 20,000 per QALY in general and/or a cost-effectiveness acceptability curve shows that the probability that the cost-effectiveness ratio remains below € 20.000 is high. Moderate evidence (*) was defined as follows: three or more studies show cost-effectiveness, defined as cost per QALY below € 20,000, but the range of CEA ratios may exceed the threshold value of € 20,000 and/or some studies show a point-estimate in the Base Case analysis that exceeds € 20,000 per QALY and/or a cost-effectiveness acceptability curve shows a considerable probability that the cost-effectiveness threshold exceeds € 20,000 per QALY.

- *for studies reporting in terms of benefit to cost ratio:*
Especially in the US, many studies report on cost-effectiveness in terms of benefit to cost ratios. These studies, in general, only pay attention to the financial effects of an intervention, by comparing the investments to be made with the financial gains, for instance, in terms of savings on future healthcare costs for disease or in terms of productivity gains. These studies, in general, assume health benefits of the intervention under study. In these studies, a benefit to cost ratio > 1 reflects cost-effectiveness. These studies were included if all important costs were taken into account. If all available studies reported a benefit to cost ratio > 1, ** stars were awarded (strong evidence for cost-effectiveness). In a situation where benefit to cost ratios were below 1 as well, the cost-effectiveness evidence was assessed as being moderate

- *for studies reporting in terms of cost per case averted:*
Many studies, especially in the field of infectious diseases prevention, report cost-effectiveness in terms of costs per case averted. It is not easy to translate this figure to cost per life year gained or cost per QALY gained instantly. Often, an averted case at a young age has more health benefits than an averted case at older age. Again, this type of ratio only pays attention to the financial costs and benefits of an intervention, while not including benefits in terms of life years gained. Here, an attempt was made to relate the cost per case averted to the anticipated costs of one case, preferably using data from the Dutch Cost of Illness Study (Slobbe et al., 2006). With this type of reporting on cost-effectiveness, ** stars were used for cost-effectiveness (strong evidence for cost-effectiveness) if the cost per case averted was constantly below the expected cost figures for a disease case, one * (moderate evidence for cost-effectiveness) was given when the cost-figures also exceeded the expected cost figures for a case.

Cost-effectiveness ratios from foreign studies are transferred to the Euro and recalculated to the year 2005. The background tables in Appendices 6 and 7 both show the costs in terms of original currency and the recalculation to 2005 Euro. For the recalculation to 2005 Euro, OECD Health Data was used (OECD, 2005).

2.2.6 Criteria for transferability to Dutch situation

Since the literature is mainly based on international studies, it is not possible to directly generalize the results to the Dutch situation. Therefore experts in the field of the prevention programmes under study were asked to discuss the translational issue. This interview was done with a semi-structured questionnaire (see Appendix 3). At least two field experts for every intervention were interviewed. The purpose of the interviews was also to detect economic evaluations that were not found by the literature search described above. The transferability of the foreign economic evaluations to the Dutch situation was either scored as 'without major problems' (**) if the results could be easily transferred or as 'with major problems' (*) if there are major problems with transferability of foreign study results to the Dutch situation and more research in the Dutch context is warranted.

2.2.7 Criteria for implementation in the Netherlands

The same experts were also asked to discuss the implementation aspects and possibly, ethical aspects of the interventions. The experts were asked whether implementation of the intervention in the Netherlands was practically, financially and ethically feasible. The questions on implementation issues are summarized in Appendix 3. In gathering this information, we tried to establish a balanced point of view and not just a simple opinion. However, due to time restraints it was not possible to interview a large number of people and the information described in this report is for a great part the opinion of a few experts. Implementation was considered to be good (**) if no problems with respect to implementation were expected and moderate (*) if some or major problems were expected with regard to implementation in the Netherlands. These problems can concern organizational or infrastructural issues, for instance in a situation where no adolescent vaccination moment was introduced in the National Immunization Programme before, or ethical issues, for instance resistance within society to mandatory fortification of staple foods.

2.2.8 Summary of scoring system used

All interventions selected are assessed on the following three aspects: cost-effectiveness, transferability of foreign study results to the Dutch context and implementation issues. A two-star system is used for each item, where two stars rewarded reflect the most positive situation.

For **cost-effectiveness** the stars represent:
* Moderate evidence: three or more studies show cost-effectiveness, defined as:
- The range of possible values (either from sensitivity analyses or uncertainty analyses) often exceeds the threshold value of € 20,000 per QALY/LYG and/or some studies show a point-estimate in the Base Case analysis that exceeds € 20,000 per QALY/LYG and/or a cost-effectiveness acceptability curve shows a considerable probability that the cost-effectiveness threshold exceeds € 20,000 per QALY.
- Benefit to cost ratios < 1 are reported.
- Costs per case averted above the expected cost per case are reported.

** Strong evidence: three or more studies show cost-effectiveness, defined as:
- The range of possible values of the cost-effectiveness ratio (either from sensitivity analyses or uncertainty analyses) does not exceed € 20,000 per QALY/ LYG and/or a cost-effectiveness acceptability curve shows that the probability that the cost-effectiveness ratio remains below € 20,000 is high.

For **transferability** the stars represent:
* Major problems with transferability of foreign study results to the Dutch situation, more research in the Dutch context is necessary.
** Results of foreign studies can easily be transferred to the Dutch situation.

With respect to **implementation issues** the stars represent:
* Some or major problems were expected with regard to organizational / infrastructural issues and/or ethical concerns.
** It is anticipated that implementation of the intervention in the Netherlands is feasible, implying no major problems with regard to organizational / infrastructural issues and/or ethical concerns.

3. Results: newly identified preventive interventions

3.1 Screening for neonatal group beta streptococcal infections

3.1.1 Description of health problem

Group beta streptococcus (GBS) is a normal body commensal in adults. About 20% of all pregnant women are GBS carriers, and 50% of the carriers transmit the bacteria to their babies during delivery (Trijbels-Smeulders et al., 2002; NVOG, 1998). About 2% of the infected newborns develop GBS disease within the first seven days of life (early-onset disease, EOD). The estimated incidence of early-onset GBS disease in the Netherlands is 1.9 per 1000 livebirths (i.e. approximately 400 newborn infants per year) (Trijbels-Smeulders et al., 2002). GBS disease is an important cause of morbidity and mortality in newborns. The three most common clinical presentations include sepsis, pneumonia and meningitis (Law et al., 2005). In the Netherlands, the estimated mortality rate among neonates with EOD is 5% (Trijbels-Smeulders et al., 2002), and circa 30% of the survivors suffer from permanent disability due to hypoxia (e.g. hearing or visual loss or mental retardation) (NVOG, 1998).

3.1.2 Description of intervention and current situation in the Netherlands

Prevention of early-onset GBS disease is aimed at the identification of mothers deemed to be at risk of transmitting GBS to their offspring. Treatment with intrapartum antibiotic prophylaxis (IAP) was shown to be effective in preventing early-onset GBS disease (Law et al., 2005). Various strategies to select the sub-group of high-risk women who should receive IAP were proposed. These strategies include a risk-based strategy, a screening-based strategy, a combined screening/risk-based strategy, and the Dutch strategy:

- With the risk-based strategy (used in the US), IAP is offered to all women with recognized risk factors for early-onset disease (i.e. previous infant affected by EOD, GBS bacteruria detected during current pregnancy, pre-term labor (<37 weeks), pre-labor rupture of membranes >18 hours and/or fever in labor (>38°C)). It is estimated that this approach results in 25% of the women being offered IAP, and an incidence reduction of 50-69% (RCOG, 2003; Van den Akker-Van Marle et al., 2005).
- The bacteriological screening-based strategy involves taking vaginal and rectal swabs of every woman between 35-37 weeks of gestation. All women carrying GBS (estimated as 20% of all pregnant women) and all women of whom the test results are not yet known (pre-term birth) are offered IAP. This approach is estimated to result in 27% IAP, and 78-86% incidence reduction (RCOG Guideline, 2003; Van den Akker-Van Marle et al., 2005).
- The combination strategy in which all women are screened with swabs as described in the bacteriological screening-based strategy while IAP is offered only to GBS carriers with one or more known risk factor(s) (see risk-based strategy), and not to those without risk factors. This strategy is estimated to result in 3% IAP, and 51-56% incidence reduction (Shah et al., 2001; Van den Akker-Van Marle at al., 2005).

- The Dutch strategy was introduced in the Netherlands in 1998 by the Dutch Society of Obstetricians and Gynaecologists (NVOG) and the Dutch Society of Pediatricians (NVK). This strategy is similar to the risk-based strategy, but does not include the two risk factors pre-term labor < 37 weeks and pre-labor rupture of membranes >18 hours. When these two risk factors are present, a vaginal and rectal swab is taken to determine GBS colonization. IAP is offered when an intrapartum culture is positive (NVOG guideline 1998). This strategy is estimated to result in a 20% reduction of incidence of GBS infection of newborns (Van den Akker-Van Marle et al., 2005). The incidence of proven EOD sepsis decreased from 0.54 per 1000 livebirths in 1997-1998, to 0.36 in 1000 in 1999-2001 after the introduction of this guideline. The incidence of meningitis and the case fatality rate did not decrease (Trijbels-Smeulders, submitted).

3.1.3 Results from economic evaluation studies

Based on literature search and interviews with field experts ten studies were identified of which seven studies were included in this study (Appendix 6, Table 6.1). One of the included studies was conducted in The Netherlands. Van den Akker-Van Marle et al. (2005) calculated the cost-effectiveness of the four above mentioned prevention strategies of GBS disease in the Netherlands. The authors concluded that the risk-based strategy was the most cost-effective prevention strategy, with € 7600 per QALY gained. The combined screening risk-based strategy has comparable results, with € 9100 per QALY gained. The combination strategy has also the advantage that less pregnant women have to be treated to prevent a GBS case (62 instead of 101 in the risk-based strategy). The current Dutch guideline and the screening-based strategy were estimated to have a cost-effectiveness ratio at € 48,800 per QALY and € 59,300 per QALY, respectively. The polymerase-chain-reaction (PCR) test could accelerate the time of determining the colonization of GBS in pregnant women. The test takes about 30-45 minutes instead of two days with the current method. The combination strategy with PCR would be very cost-effective with € 2300 per QALY gained.
Stan et al. (2001) compared the current strategy of Geneva University Hospital (Switzerland) to the risk-based strategy and the screening-based strategy. The risk-based strategy will prevent 69 streptococcal sepsis cases per million deliveries and the costs per averted sepsis case would be £ 60,700. Furthermore, the number needed to treat to prevent one sepsis would be 1087. The screening-based strategy would prevent 102 cases of sepsis per million deliveries and the costs per averted sepsis case would be £ 473,600. The number needed to treat is 1029 to prevent one sepsis case. The portion women receiving IAP would increase from 6% (current policy), to 13.5% (risk-based strategy) or 16.5% (screening-based strategy).
In Mohle-Boetani et al. (1999) the cost and health benefits of a risk-based strategy in Northern California, US were estimated. If the adherence to the guidelines was 100%, 17% of the mothers would receive IAP at the cost of $ 490,000. $ 1.6 million would be saved by preventing 66 GBS cases (64% reduction). The net savings would be $ 1.1 million and 61 life-years would be gained in this strategy. If asymptomatic term infants of mothers who received IAP were observed for 48 hours, instead of 24 hours, there would be an additional cost of $ 9.2 million. This would increase the cost per life-year saved to $ 130,000.
Benitz et al. (1999) evaluated five strategies to prevent early-onset GBS disease in the US. The screening-based strategy where a culture is taken at 28 weeks would prevent 32.9% of the EOD cases and the cost per case prevented would be $ 22,215. The risk-based strategy would prevent 53.8% of EOD cases and would cost $ 3067 per case prevented. Screening at 35-37 weeks instead of 28 weeks would prevent 75.1% of the EOD cases and the costs would be $ 11,925 per case prevented. The combination strategy would prevent 75.6% of the EOD

cases and cost $ 9720 per case prevented. Universal IAP would prevent the most GBS cases: 80.2%. It would cost $ 12,049 per case prevented.
Garland et al. (1995) evaluated three strategies for preventing EOD in large teaching hospitals in Australia. With the screening strategy cultures were taken at 28 weeks. 46% of all EOD cases would be prevented and the cost per case prevented would be $ 6663. The benefit cost ratio would be 1.33:1 In the combination strategy 38% of the cases would be prevented with costs of $ 7416 per case prevented. The benefit cost ratio would be 1.09:1. In the risk-based strategy 80 cases would be prevented. The cost would be $ 270 per case prevented and a benefit-cost ratio of 56.42:1. In conclusion, the risk-based strategy would be the most cost-effective strategy.
Yancey et al. (1994) evaluated the effects and cost of several screening methods in the US. In the screening strategy, with taking a culture at 26-28 weeks, the costs would be $ 11,900 per case averted. In the combination strategy cost would be $22.900 per case averted. Other screening methods were also evaluated but the used tests were found to be unreliable (rapid test instead of a culture for detection of GBS).
Mohle-Boetani et al. (1993) compared the outcomes and costs of several prevention strategies versus no intervention from a societal perspective in the US. The screening strategy would prevent 3300 cases (47% of neonatal disease) and could save $ 16 million in direct medical costs. Cost per case prevented would be $ 28,800 with a benefit cost ratio 1.2:1. The risk-based strategy would prevent 3200 cases and the net savings would be approximately $ 66 million. Cost per case prevented would be $12.900 with a benefit cost ratio of 2.6:1.

3.1.4 Transferability of foreign study results to Dutch context

The validity of the included foreign studies for the Dutch situation is limited. First of all, in most developed countries most women give birth in the hospital. Therefore, in contrast to the Netherlands, no additional costs for hospitalization for prevention have to be accounted for. Furthermore, the point in time when a culture should be taken differs between studies. In the older studies (Garland et al., 1995; Yancey et al., 1994; Benitz et al., 1999; Mohle-Boetani et al., 1993) screening occurs at 26 to 28 weeks' gestation instead of 35-37 weeks' gestation, as assumed in the more recent studies. If prenatal screening takes place relatively early in pregnancy, GBS colonization later in pregnancy can be missed. In Benitz et al. (1999) screening took place at 28 weeks or at 35-37 weeks and showed that screening at 28 weeks prevents 33% of the EOD cases and screening at 35-37 weeks prevents 75.1% of all EOD cases. The current (international) standard is to screen at 35-37 weeks of gestation. Another factor that hampers the ability to generalize the results of foreign studies to the Dutch situation is the assumption on the magnitude of the relative risk. A recent study in the Netherlands concluded that the case fatality rate of early-onset GBS disease in the Netherlands is approximately 5% (Trijbels-Smeulders et al., 2002) but other studies sometimes used a higher mortality rate of 20%. Finally, the strategies described in the publications differ from each other even though they are named the same. For instance, in the screening-based strategy described in Van den Akker-Van Marle et al. (2005) IAP is given to all cases of (unscreened) pre-term labor. In Stan et al. (2001) IAP is given according to the risk-based strategy if no culture results are available. This implies that less IAP is given in the strategy of Stan et al. (2001) compared to the strategy in Van den Akker-Van Marle et al. (2005). In conclusion, there are many differences between foreign studies and the Dutch situation. This limits the transferability of those results to the Netherlands. However, there is a good-quality Dutch study available that estimates the cost-effectiveness ratios of the different strategies to prevent GBS disease within the Dutch context.

3.1.5 Feasibility of implementation in the Netherlands

It seems that the current guideline for the prevention of early-onset GBS disease is not (cost) effective at this moment (Van den Akker-Van Marle et al., 2005; Trijbels-Smeulders et al.,). Other strategies that are currently available are the screening-based strategy, the risk-based strategy and the combination strategy. The risk-based strategy differs from the current Dutch guideline in offering prophylaxis without screening when specific risk factors are present (i.e. pre-term labor or pre-labor rupture of membranes >18 hours). Both strategies have, however, the disadvantage that in 40-50% of all cases of EOD no maternal risk factor is present. The combination strategy has this disadvantage as well. In this strategy, only women who are carrier of GBS and have one or more risk factors are given prophylaxis. An advantage of this strategy is that less pregnant women receive antibiotics. Furthermore, obstetricians will be more alert to react on risk factors when a woman is carrier of GBS. A consequence of implementation of the combination strategy may be that after prenatal diagnosis women will demand the antibiotics when test results show that she is carrier of GBS. If this happens, it may possibly lead to a bacteriological screening approach. With the bacteriological screening approach, theoretically all GBS carriers receive prophylaxis during labor which will prevent vertical transmission and thereby EOD with the newborn. This strategy would, however, have major consequences for the unique obstetric system in the Netherlands. Approximately 30% of the pregnant women deliver at home (in 2000). Prophylaxis can only be offered in hospital setting, so all carriers of GBS would have to deliver in the hospital (30,000 women). Apart from the increase in costs induced by the increase in hospital births, this may lead to more medicalization of the pregnancy. Finally, the increase in prescription of antibiotics will lead to higher resistance of bacteria against antibiotics in long term and increasing incidence of neonatal infections by other bacteria, such as E. coli bacteria.

The combination strategy with PCR will be the most cost-effective prevention strategy in the Netherlands (Van den Akker-Van Marle et al., 2005). Accordingly, most health professionals are in favour of the combination strategy as best prevention strategy against GBS disease (based on a poll during a recent symposium entitled ‘Prevention of neonatal group B streptococcal disease: Which strategy in the Netherlands?’). This could, however, change with future developments. Vaginal disinfection with chlorhexidine could be a simple, cheap and safe alternative for the prevention of early-onset GBS disease (Adriaanse et al., 1995).

3.1.6 Summary

About 2 in 1,000 newborns develop early-onset group Beta streptococcal disease. Prevention of this disease starts with identifying pregnant women at risk of transmitting GBS to their offspring. Four different strategies for this selection were proposed: risk-based strategy, screening-based strategy, combination strategy, and the Dutch strategy. The current Dutch strategy in the prevention of GBS disease seems to be not cost-effective. The combination strategy seems the most cost-effective (< € 10,000/QALY) and feasible method to implement as prevention strategy for GBS in the Netherlands.

Cost-effectiveness: **
Transferability:*
Implementation: **

3.2 Universal hepatitis B vaccination

3.2.1 Description of the health problem

Hepatitis B is a contagious viral infection caused by hepatitis B virus (HBV). HBV is transmitted via blood, body fluids or at birth. The course of an acute infection varies, from temporary to fatal, from asymptomatic to symptoms as tiredness, fever, joint complaints and jaundice. Acute infection can lead to a persistent chronic infection with clinical symptoms (caused by liver damage), or, more frequently, to a sub-clinical form of the disease (Van de Laar et al., 2005). There is a strong relation between age and the course of an acute infection: 1-10% of infected young children (<6) and 30-40% of older children and adults have symptoms (Van de Laar et al., 2005). Young children are at greatest risk of a chronic infection; over 90% of those children infected at birth develop a chronic infection. Chronic carriers stay infectious to others and have an increased chance of developing long term sequelae, such as cirrhosis and hepatocellular carcinoma (Van de Laar et al., 2005).

Worldwide, about 350 to 400 million people are chronically infected with HBV (Kowdley, 2004) and every year more than a million people die of hepatitis B infection. However, the regional prevalence of HBV varies tremendously. In Southeast and Far East Asia countries over 10% of the population is infected, while in Western Europe and North America this is less than 2% (Kowdley, 2004).
The prevalence of chronic hepatitis B in the Netherlands is generally low (about 0.4%), but is higher in risk groups such as drug users, men having sex with men and prostitutes. Also, the prevalence is alleviated in certain immigrant groups from countries with intermediate or high prevalence, e.g. mediterranean countries (Boot et al., 2005). In 2003, hepatitis B was 1,877 times reported (319 acute and 1,445 chronic infections) and the incidence of acute hepatitis B was 2.0 per 100,000 inhabitants; 3.1 for men and 0.9 for women (Van de Laar and Op de Coul, 2004; Koedijk et al., 2005).

3.2.2 Description of the intervention and the current situation in the Netherlands

Prevention of hepatitis B is possible by vaccinating those groups of people not yet exposed to the virus[1]. Since 1986, safe and effective vaccines are available. The vaccine used nowadays in the western world is a recombinant sub-unit vaccine of the hepatitis B (pre)-Surface protein (HBsAg). Adverse events of hepatitis B vaccination are usually mild, of short duration and have the same frequency as in placebo recipients (Boot et al., 2005). Standard hepatitis B vaccination consists of three vaccinations with an interval of respectively one and at least five months between the consecutive vaccination doses. In 90-95% of vaccinated cases, this leads to an adequate and lasting (> 15 years, possibly lifelong) protection.

There are two different ways of vaccination: universal (a whole cohort receives vaccination regardless of individual risks) and selective (only high risk groups). In 1992, the WHO recommended that universal vaccination against HBV (of infants or adolescents) should be integrated into all national immunization programmes. Most European countries have done so, but the Netherlands and some other countries with a very low (<1%) HBV carrier prevalence (United Kingdom, Ireland and the Scandinavian countries) decided not to start an

[1] See De Melker HE, Gerritsen AAM, Hahné SJM (Eds.) for further discussion on this subject.

universal vaccination programme. It was estimated that in the Netherlands universal immunization of infants could only prevent 5-10% of new carriers of HBV, because most newly infected persons came from abroad (Kretzschmar et al., 2002).

The current Dutch hepatitis B prevention policy consists of four (voluntary and for free) selective programmes:

- Screening of all pregnant women and vaccination of children of infected mothers (since 1989).
- Vaccination of persons who are at increased risk to be infected or to infect others with hepatitis B through work-related situations (e.g. surgeons, nurses, dentists) or through their living circumstances (e.g. mentally disabled people living in institutions) (since 2000).
- Vaccination of all newborn children with one or two parents from a medium or high HBV prevalence region. This is integrated into the National Immunization Programme (since 2003).
- Vaccination of four high risk groups, namely men having sex with men, heterosexual persons who change sex-partners frequently, hard drug users and commercial sex-workers. This programme started in 2002 as a catch-up campaign for a four-year period, intended to reach as many members of target groups as possible. Recently, it was decided that this programme will be continued for a longer period.

In spite of the four selective programmes, at this moment the vast majority of the Dutch population is not protected against hepatitis B. As part of its permanent advisory role on the contents and organisation of the National Immunization Programme, the Health Council of the Netherlands is expected to review the current Dutch hepatitis B prevention policies in the near future.

3.2.3 Results cost-effectiveness studies

The description of the cost-effectiveness of universal hepatitis B vaccination is based on seven studies (Appendix 6, Table 6.2). Six of them are European studies, one is from the Netherlands. All studies are based on simulation models, but the assumptions, time span and methodology used in the studies differ, and therefore, results differ as well. Outcome measures used were life years gained (LYG) or cases prevented.

The studies compared universal vaccination (infants, schoolchildren, adolescents or combinations of these) with prenatal screening (De Wit et al., 2000; Wiebe et al., 1997) vaccination of risk-groups (Zurn et al., 2000; Garuz et al., 1997; Mangtani et al., 1995) or no vaccination at all (Fenn et al., 1996; Antonanzas et al., 1995).
All studies, except the Dutch study, showed that universal immunization is a cost-effective strategy in comparison with prenatal screening, vaccination of high risk groups or no vaccination at all. However there were differences in the universal strategy that was primarily recommended from a cost-effectiveness perspective. In the studies of Wiebe et al. (1997) and Fenn et al. (1996) immunization of infants is the most cost-effective strategy. The results were 15,900 Canadian Dollars per LYG respectivily 5,234 (undiscounted) or 227,130 (discounted) UK Pounds per LYG. Four studies found that immunization of adolescents is the most cost-effective strategy. Both the results of Garuz et al. (1997) and Antonanzas et al. (1995) were presented per cases prevented and were 603 (undiscounted) or 850 (discounted) US Dollars, respectivily 49,000 (undiscounted) or 82,000 (discounted) Spanish Pesetas. In the study of Zurn et al. (2000) universal vaccination of adolescents costs 53,970 Swiss Francs

per LYG. This is 2,824 (undiscounted) or 51,817 (discounted) UK dollars per LYG in the study of Mangtani et al. (1995).
The Dutch study modelled the cost-effectiveness of adding universal vaccination of infants to the prenatal screening programme. Due to the relative high percentage of HBV infections imported by immigrants, universal vaccination of infants had almost no effect on the prevalence and infection pressure on susceptible persons and only a small impact on prevention of long-term complications of hepatitis B. So in this study, universal vaccination was not a cost-effective strategy.
All studies included some form of sensitivity analysis to assess the effects of key parameters on the estimated outcomes. In general, sensitivity analyses indicated that vaccination costs, the effectiveness of vaccination, prevalence and the discount rate had the largest impact on the cost-effectiveness. In the Dutch study universal immunization of infants became more cost-effective with lower vaccine costs and lower discount rate of health benefits in the future (De Wit et al., 2000). At present, the Dutch cost-effectiveness analysis is being updated. Several major changes in assumptions are now made compared to the study that was published in 2000, including (much) lower costs of vaccination, lower discount rates for effects of vaccination, and the inclusion of a third route of transmission, namely horizontal transmission at children's age. Preliminary results of the updated analyses show that universal vaccination of both infants and adolescents have cost-effectiveness ratio's that remain below the threshold of € 20,000 per QALY (De Wit et al., in preparation).

Beutels (2001) reviewed recent (1994-2000) economic studies of hepatitis B vaccination. He concludes that economic evaluations of vaccination in very low-endemic areas have yielded contradictory results and therefore evidence is inconclusive. Beutels makes clear that the different results are partly determined by differences in modelling techniques and differences in assumptions made in the different studies. For example, using a static model to estimate the effectiveness of vaccination at population level underestimates the cost-effectiveness of vaccination in comparison to a situation where cost-effectiveness is modelled using a dynamic model. According to Beutels (2001) vaccination of adolescents seems most cost-effective for low-endemic countries, because the period between vaccination and start of sexual activity (the major route of infection in low-endemic countries) is relatively short.

3.2.4 Transferability foreign study results to the Dutch situation

Translation of the foreign studies to the Dutch situation has several limitations. First and most important, the countries of the study differ in endemicity. The level of prevalence of hepatitis B in a country is a key-parameter in determining the cost-effectiveness of universal immunization, because vaccination is by definition more cost-effective in high-prevalence regions. The prevalence in the Netherlands is very low, less than 1%. Only in the two studies of the United Kingdom, the prevalence is comparable to the Dutch situation. In the other countries, in particular Spain, the prevalence is higher so universal immunization has more effect and is more cost-effective than in the Netherlands. Besides the prevalence, the countries studied differ in other aspects (e.g. transmission route and vaccination rate) from the Dutch situation. In the Netherlands nowadays most HBV is transmitted by male homosexual contact, while in some other countries intravenous drug use is still an important transmission route. In addition, since the studies were published, vaccine prices dropped considerably. Also, immigration patterns, and therefore the proportion of imported infections, changed. These differences between countries have major impact on the estimated cost-effectiveness of vaccination strategies. The ongoing Dutch evaluation study of hepatitis B vaccination strategies takes these changes into account (De Wit et al., in preparation).

3.2.5 Feasibility of implementation in the Netherlands

At present, the Health Council of the Netherlands discusses the necessity of changing the current risk-based strategy to prevent hepatitis B to a strategy that includes universal vaccination, either of infants or of adolescents. Vaccination of newborns from infected mothers and infants with one or two parents from a medium or high HBV prevalence region is already integrated in the National Immunization Programme (NIP). Until April 2006, this used to be done with three separate injections of hepatitis B vaccine. However, since April 2006, universal infant pneumococcal vaccination was introduced in the National Immunization Programme. To avoid giving three different injections to a child at any one moment, a combination vaccine containing DTP-IPV-HepB-Hib is being used for those children with one or two parents from endemic regions. This commercial combination vaccine is relatively expensive in comparison with the DTP-IPV-Hib vaccine that was used before. The undesirability of three different vaccinations at one moment and the relatively high price of the commercial combination vaccine including hepatitis B vaccine might hamper the introduction of hepatitis B vaccination for all infants in the short term.

As the Dutch National Immunization Programme traditionally was targeted at infants and young school children, universal vaccination of adolescents would require the introduction of an entirely different age group within the NIP. Many issues surround such a major change in the NIP. At this moment, it is unclear how a succesfull vaccination programme for adolescents can be achieved and preserved. Should it be organized through schools or through municipal health services? Who needs to give informed consent, only parents or the adolescent as well? Will vaccination against a (mainly) sexually transmitted disease be accepted widely? Will the acceptance of and compliance with vaccination be sufficient to decrease transmission of the virus at population level? These and other issues need to be resolved before a major change in the NIP can be implemented. Because other vaccines, such as pertussis vaccine (see section 3.4) and human papilloma virus vaccine (see section 3.5), also qualify for vaccination of adolescents, it is expected that the Health Council committee will reflect upon the possibility of implementation of adolescent vaccination in the Netherlands.

3.2.6 Summary

Hepatitis B is a contagious viral infection transmitted via blood, body fluids or at birth. In the Netherlands the prevalence of hepatitis B is generally low, but higher among some groups (men having sex with men, prostitutes, drugusers) and some immigrant groups. Because of the very low endemicity, the Dutch government decided not to implement universal vaccination, but to implement risk-based prevention policies, including vaccination of risk-groups. Economic evaluations in very low-endemic areas have yielded contradictory results on the cost-effectiveness of such policies, therefore evidence is inconclusive. For low-endemic countries, vaccination of adolescents seems more cost-effective than vaccination of infants. Because the Netherlands differs from the countries studied in for example prevalence, transmission route and vaccination rate, translation from the international results to the Dutch situation is difficult. However, preliminary results of an ongoing study on cost-effectiveness of different vaccination strategies for the Netherlands show that both infant vaccination and adolescent vaccination are cost-effective. Implementation of universal vaccination in the Netherlands is not without problems. The undesirability of three different vaccinations at one moment and the relativily high price of the commercial combination (DTP-IPV-HepB-Hib) vaccine might hamper the introduction of hepatitis B vaccination for all infants. Universal vaccination of adolescents would require the introduction of an entirely different age group

within the NIP. Such a major change in the NIP is surrounded with many issues that need to be resolved

Cost-effectiveness *
Tranferability *
Implementation *

3.3 Rotavirus vaccination of newborns

3.3.1 Description of health problem

Rotaviruses are the most common cause of severe gastroenteritis in infants and young children. It causes fever, diarrhea, and vomiting. Because of the risk of dehydration, a rotavirus infection can be fatal (especially in developing countries). The transmission route is mainly faecal-oral. Other routes are via aerosols and other body fluids. Transmission can also occur via contaminated water or food. The incubation period is approximately two days. Symptoms usually accompany primary infection, which is followed by protection against subsequent rotavirus infections. For this reason, the peak attack rates for symptomatic rotavirus disease occur in children between 6 and 12 months of age.

In the Netherlands rotavirus infection in children is seasonal, with highest incidence in winter months. The annual incidence of rotavirus infections is approximately 190,000, of which 58,000 in children younger than five years of age (Kemmeren et al., 2006).
About 3,400 children younger than five years are hospitalized for rotavirus each year (this includes infections that are acquired in hospitals). Infections are estimated to be fatal in approximately two to three of all hospitalized rotavirus cases younger than five years (Mangen et al., submitted).

3.3.2 Description of intervention and current situation in the Netherlands

Current prevention measures in the Netherlands to counteract transmission of rotavirus consist of hygiene guidelines at day-care centers, primary schools, hospitals and nursing homes. Once infected with rotavirus, consequences of diarrhea and vomiting are treated, not the virus itself. Treatment is targeted towards the prevention of dehydration. For prevention of rotavirus infection, two oral live-attenuated rotavirus vaccines are available: RotaRix® and RotaTeq®. RotaRix® was licensed in the Netherlands in March 2006[1]. The licensure for RotaTeq® was approved by the European Union in June 2006. Both vaccines target the most found rotavirus serotypes G1-G4. The RotaRix® vaccination was estimated to reduce rotavirus gastroenteritis induced hospitalization for at least one night by 85% (Ruiz-Palacios et al., 2006). The vaccine efficacy of RotaTeq® against office or clinical visits for rotavirus gastroenteritis was estimated to be 86% (Vesikari et al., 2006). For both vaccines, no increase in serious bowel blockages (intussusception) was noted among recipients of the vaccine versus placebo (Ruiz-Palacios et al., 2006; Vesikari et al., 2006). A former vaccine, Rotashield®, was withdrawn from the US market within one year of its introduction because of its association with intussusception.
Both rotavirus vaccines are intended to be given to infants at the same time as their immunizations for diphtheria-pertussis and tetanus, which are currently included in the

[1] See De Melker HE, Gerritsen AAM, Hahné SJM (Eds.) for further discussion on this subject.

National Immunization Programme. RotaRix® and RotaTeq® are administered as an oral liquid in buffer as two doses (Rotarix®) or three doses (RotaTeq®) to babies, with the first dose given at 6-14 weeks of age.

3.3.3 Results from economic evaluations

The description of the cost-effectiveness of rotavirus vaccination is based on five studies (Appendix 6, Table 6.3). These studies are based on data for the Rotashield® vaccine (withdrawn from the market, as described above) and not on data for the new vaccines. However, given the similarities in efficacy, the results are expected to be generally applicable to the new vaccines (Walker and Rheingans, 2005). The first economic evaluations of the new rotavirus vaccinations are appearing at present, but until now these studies are targeted at developing countries.

All studies compared vaccination against rotavirus with no intervention. Two of the studies were performed using data from randomized, double-blind, placebo-controlled trials. Other studies were model-based. The studies either conclude that vaccination is cost-neutral (Griffiths et al., 1995; Takala et al., 1998; Tucker et al., 1998) or that the vaccine is even cost-saving (Smith et al., 1995; Carlin et al., 1999). All studies used a societal perspective; some studies included the health-care perspective as well (Carlin et al., 1999; Smith et al., 1995; Tucker et al., 1998). All studies estimated the break-even price, computed by appointing what cost of the vaccine infers economic neutrality (costs to deliver the vaccine are equal to the costs the vaccine saves in treatment costs averted and productivity losses averted). As the future vaccine price was unknown in all studies, the studies calculated net costs either by using a range of vaccine prices or by estimating the threshold price at which vaccination would be cost-neutral. Besides the break-even price, some studies also estimated the cost per event avoided (Smith et al., 1995; Tucker et al., 1998; Carlin et al., 1999). Studies differ from each other with respect to assumed incidence rates of rotavirus, vaccine efficacy, and costs of the vaccine. Cumulative incidence rates of rotavirus diarrhea in the first five years of life ranged from 55% to 85%. Different estimates of rotavirus vaccine efficacy ranging from 50% to 95% were used in the studies. The price per dose of rotavirus vaccine ranged from US$ 0.45 to US$ 30. All of the studies included some form of sensitivity analysis to assess the effects of key parameters on the estimated outcomes. Most studies included efficacy and vaccine price in their estimates. From these sensitivity analyses, it appeared that especially the costs of the vaccine and loss of productivity (work hours lost by parents) affected the break-even price of the rotavirus vaccine. Discounting was not undertaken in studies of Takala et al. (1998), Carlin et al. (1999) and, Griffiths et al. (1995). The authors justified this by stating that the major part of rotavirus hospitalizations occurred before the age of two years. As this was a relatively short time frame, no discounting was applied.

3.3.4 Transferability of foreign study results to Dutch context

There are several threats to the transferability of foreign study results on the cost-effectiveness of the rotavirus vaccine within the Dutch situation. Firstly, it is likely that the amount of workdays lost in The Netherlands will be substantially lower than assumed in foreign studies (Mangen et al., submitted). In a societal perspective, more workdays lost justify higher vaccine costs. Because work absence is relatively low in the Netherlands, the vaccine costs should be low in order to reach outcomes that are cost-neutral. However, the first information on vaccine prices does not point in that direction. Parashar et al. (2006) reported a cost price of US$ 69 per dose for RotaTeq®, which is US$ 207 for three doses.

This price exceeds the prices that are presumed in the studies on cost-effectiveness of rotavirus vaccination. Foreign studies show that vaccine price is a major factor that determines whether a rotavirus vaccination programme is cost-effective or not. A decrease in the vaccine costs is needed before introduction of rotavirus vaccines in the Dutch National Immunization Programme (NIP) would become cost-effective. This is also concluded in a forthcoming study on the cost-effectiveness of introduction of rotavirus vaccine in the NIP (Mangen et al., submitted). Secondly, the incidence of rotavirus in the Netherlands is lower than in countries in which the regarded studies took place. The incidence of rotavirus is important for the estimated effectiveness and associated cost-savings of averted infections of vaccination. Therefore it can be expected that vaccination is less cost-effective in the Netherlands. Thirdly, in the consideration of including rotavirus vaccination in the National Immunization Programme it would be important to have better insight into circulating rotavirus strains in the Netherlands. The current vaccines are focused on G1-G4 serotypes. These are also the most commonly found strains in the Netherlands (Van der Heide et al., 2005), but in the past decades other serotypes have emerged, especially the G9 rotaviruses. In 2006, also a new rotavirus, G12, was identified in the Netherlands.

3.3.5 Feasibility of implementation in the Netherlands

Because oral rotavirus vaccine can be given at the same time as simultaneously administered routine infant vaccines, mass vaccination could be relatively easy to implement in the Netherlands. As the RotaRix® vaccine should be administered at two and four months, the vaccination can be combined with vaccination against diphtheria-tetanus-polio-*Haemophilus influenzae* type b and pneumococcal disease. RotaTeq® requires an additional session in the National Immunization Programme. No observation is made that either of the two vaccines would affect the immune response of simultaneously administered routing infant vaccines (Parashar and Glass, 2006). However, implementation of rotavirus immunization at current sessions implies that the current maximum of two vaccines per session would have to be exceeded.
A substantial reduction in morbidity from childhood gastroenteritis would be expected, although the impact on mortality in the Netherlands is likely to be limited. As parental perceptions of the severity of disease have always been strongly associated with high coverage of vaccination, there was concern that the vaccine would not be acceptable to parents in the Netherlands (Van de Bovenkamp-Meijer and Rümke, 2005). This could possibly have an impact on uptake of vaccination against other diseases as well.

3.3.6 Summary

Rotaviruses are the most common cause of severe watery diarrheal disease in infants and young children. Several economic evaluations conclude that rotavirus immunization would be cost-neutral or even cost-saving. Although these results are based on data on the former vaccine Rotashield®, the results are expected to be generally applicable to two new vaccines that recently became available (RotaRix® and RotaTeq®). However, it can be expected that vaccination is less cost-effective in the Netherlands, because rotavirus incidence is lower, vaccine costs are higher and work absence of parents is less than assumed in foreign studies. Mass rotavirus vaccination could be relatively easy implemented in the Netherlands. As rotavirus vaccination is available in an oral variant, implementation would not be associated with the necessity to increase the number of injections at one moment. However, it remains questionable whether this vaccine is acceptable to parents who perceive a rotavirus infection to be a relatively innocent disease.

Cost-effectiveness: *
Transferability: *
Implementation: *

3.4 Pertussis vaccination of adolescents

3.4.1 Description of the health problem

Pertussis or whooping cough is a highly contagious disease of the respiratory tract and is transmitted by coughing (Mooi et al., 2005; De Boer et al., 2005). In coughing patients the contagiousness may last for three weeks after the onset of symptoms. Someone without overt symptoms can still be infectious. Symptomatic pertussis starts as a normal cold, sometimes with fever. After one to two weeks typical symptoms develop, like severe coughs, which last for at least two weeks. These severe coughs can be accompanied by cyanosis, apnoea and fever. The most prevalent complications of pertussis are secondary infections, such as inflammation of the middle ear or of the lung (>20%), or affected function of the brain (1%). Particularly in young children, the disease can cause severe complications and babies can die from it (Mooi et al., 2005; De Boer et al., 2005).

After the implementation of pertussis vaccination in 1952 the number of children with pertussis decreased (Mooi et al., 2005). In the last ten years, the incidence of notified cases (total population) varied between 50.2/100,000 in 2001 and 16.0/100,000 in 1998 (De Greeff et al., 2003). Of all diseases which are part of the Dutch National Immunization Programme (NIP), pertussis has the highest incidence per person per year (De Melker et al., 2005). Based on a cross-sectional modelling study, the actual incidence of pertussis infections in the Netherlands was estimated at 6.6% in 1995 in the age category 3-79 year, with highest incidence reported in the ages of 20-24 years (De Melker et al., 2006). Infections in older adolescents and adults contribute to the transmission of pertussis to high-risk groups, especially neonates which have not yet been sufficiently vaccinated (De Melker et al., 2005). Although the number of pertussis cases in children aged 1-4 years and 5-9 years decreased – most likely due to the introduction of the booster vaccine for four-year-olds – , the number of cases among adolescents and adults increased in 2004 in comparison with 2001 (Mooi et al., 2005).

3.4.2 Description of the intervention and current situation in the Netherlands

In 1952 pertussis vaccination was introduced in the Netherlands, first as a single vaccine and later in combination with diphtheria, tetanus, polio (DTP-IPV) and Haemophilias influenza b (Hib) (De Melker et al., 2005)[1]. Currently, children are vaccinated at 2, 3, 4 and 11 months with the acellular DTP-IPV-Hib vaccine. An acellular repeating (= booster) vaccination is given at 4 years of age since the end of 2001 (see Table 3.1).
Different vaccination strategies to decrease diseases burden from pertussis were suggested (Forsyth et al., PIDJ 2005; 24: S69-S74), among them: universal adult vaccination, selective immunization of close contacts of young newborns, selective immunizations of health care workers, universal immunization of adolescents.
As mentioned before, the pertussis incidence among adolescents (10-19 years) is still increasing, leading to school absences, parental time lost from work, and extra costs for

[1] See De Melker HE, Gerritsen AAM, Hahné SJM (Eds.) for further discussion on this subject.

medical care and public health surveillance. Pertussis booster vaccination of adolescents (and adults) could possibly be useful to prevent morbidity in this age group and limit the spread of disease to susceptible individuals (herd immunity effect), particularly to infants who did not yet receive the complete cycle of five vaccines (Marchant, 2005). Several studies evaluated the role of adolescents and adults in transmission of pertussis to infants (Bisgard et al., 2004; Long et al., 1990; Izurieta et al., 1996). These studies emphasize the role of adolescents and also adults in disease transmission to infants.

Currently, pertussis vaccine is not recommended for persons older than 4 years of age in the Netherlands because of past concerns about the safety of whole-cell pertussis vaccines. Safer acellular pertussis (aP) vaccines were developed and are evaluated in adolescents and adults and determined to be safe and immunogenic (Ward et al., 2005; Strebel et al., 2001; Tran Minh et al., 1999; Rothstein et al., 1999). Currently, adolescent vaccination is recommended in the US, Canada, Australia, France, Austria, Germany, Malta and Finland (Eurosurveillance 2004;9:70) (www.euvac.net) (Halperin et al., 2005) In the Netherlands the licensed vaccine for adolescents 10 to 18 years of age is Boostrix®.
The preventive intervention examined in this section is acellular booster vaccination of adolescents (10-19 years).

3.4.3 Results from economic evaluation studies

Five cost-effectiveness studies were found in the literature (Appendix 6, Table 6.4). None of these studies was adapted to the Dutch situation. From those five studies, three had QALY or LYG as an outcome measure (Caro et al., 2005a; Lee et al., 2005; Edmunds et al., 2002), one study resulted in a clinical outcome measures, namely pertussis cases avoided (Iskedjian et al., 2004). And the fifth study looked at the break-even cost per vaccination (Purdy et al., 2004), that is the vaccine-price at which the preventive intervention would be cost-neutral to society.

The studies by Caro et al. (2005a) and Lee et al. (2005) compared the US pertussis immunization schedule (a combined acellular DTP) with or without an adolescent acellular booster dose, given specific estimates of herd immunity. In the study by Caro et al. (2005a) the cost-effectiveness ratio was $ 22,023 per life year gained (LYG) from the health care perspective and $ 6,253 per LYG from the societal perspective assuming a reduction in non-target cases (herd immunity) of 20%. Assuming a herd immunity of 5% resulted in high cost-effectiveness ratios. Herd immunity of 35% resulted in cost-savings. The authors warned that their results should be viewed with caution given the large gaps in the evidence surrounding the true incidence of typical symptomatic pertussis. Lee et al. (2005) concluded that one-time vaccination of adolescents might be reasonably cost-effective if the vaccination price is comparable to that in other countries where it was being used at that moment (Germany, Canada, Australia, France). With an incremental vaccine price of $ 15, a single-dose adolescent vaccination strategy costs $ 20,000 per QALY from the societal perspective and $ 23,000 per QALY from the health care perspective. The results were sensitive to several key assumptions: disease incidence, vaccine efficacy, vaccine-associated costs and frequency of vaccine adverse events. These parameters were varied over wide ranges because of their uncertainty. The study might have underestimated the disease incidence due to underreporting. However, at extremely high disease rates the vaccination appears more favourable in terms of cost-effectiveness. Iskedjian et al. (2004) evaluated a combined vaccination programme (CVP) including a diphtheria, acelular pertussis and tetanus (dTap) vaccine at 12 years of age in comparison with the DT immunization in Canada, Ontario at

that moment. From a Ministry of Health perspective, the combined programme costs $CAN 188 per pertussis case avoided. The programme was cost-saving from the societal perspective.
According to Purdy et al (2004) the break-even cost per adolescent pertussis vaccination was $ 36.92. They were not able to predict the long-term protection from booster vaccination or the optimal window of revaccination, because of the unclear long-term efficacy of aP vaccine in adolescents and because herd immunity is difficult to model. Edmunds et al (2002) compared an acellular pertussis booster dose at 15 years of age with no vaccination assuming different percentages of cases prevented in younger infants (20-80%). From the health care perspective the booster was only cost-effective when minimal 60% of the cases in younger infants were prevented (£ 13,019 per LYG). The results were sensitive to variations in the degree of herd immunity protection, mortality rate, degree of under-reporting, vaccine cost and the discount rate for both the costs and benefits.

The American Committee of Infectious Diseases (2006) gave an overview of economic studies in a policy statement with recommendations for pertussis vaccination among adolescents. Their conclusion is that universal, single-dose acellular DTP vaccination during adolescence is a cost-effective strategy considering a variety of assumptions like incidence of pertussis, waning (decreasing) immunity, vaccine efficacy, vaccine coverage and infant transmission. Hay et al (2005) reviewed the direct and indirect costs associated with pertussis and its complications and cost-benefit analyses of pertussis booster vaccination as mentioned before (Purdy et al., 2004; Lee et al., 2004). They concluded that vaccination of adolescents with the acellular DTP booster vaccine can be a cost-beneficial strategy. Caro et al (2005b) reviewed the studies mentioned before (besides Lee et al., 2004) and concluded that the results are inconsistent because of differences in estimates of the true incidence of pertussis and of the potential herd immunity. Further economic analyses are required (Caro et al., 2005b).

3.4.4 Transferability of foreign study results to the Dutch context

All the cost-effectiveness studies as found in the literature were from abroad. However, the uncertainties as mentioned in the foreign studies will probably be uncertain in any future Dutch study as well. The true incidence of pertussis is not known as current surveillance data will probably be underreported, since only patients that consult the general practitioner are registered. The transmission routes through which infants are infected are still unclear. Therefore, the RIVM has initiated the BINKI-Study. In this study, family members of pertussis-infected infants are tested for pertussis infection. The results of this study are expected to provide more information about the transmission patterns of pertussis.
Iskjedan et al. (2001 Pharmaeconomics) suggest that adequate coverage of the target population can be attained by coupling the acellular pertussis vaccine with the existing Canadian DT booster at adolescence age. That also keeps the administration costs to a minimum. The cost-effectiveness studies only looked at adding the booster to the DT. In the Netherlands the last DT booster is given at the age of nine years. Table 3.1 describes the pertussis immunization schedules of the countries that already introduced the adolescent booster vaccination. Nearly all these countries added an extra booster to the schedule, but only Australia replaced their former 18 months vaccination with the vaccination at the age of 15-17 years.

Table 3.1 Pertussis immunization schedules in several countries (Halperin et al., 2005)

Country	Previous schedule	Revised schedule	Product used	Implementation strategy for adolescent vaccination
The Netherlands	2,3,4,11 mo 4 yr	Not yet	Acellular DTP-IPV/Hib DT-IPV	
Canada	2,4,6,18 mo 4-6 yr	2,4,6,18 mo 4-6 yr 14-16 yr	Acellular DTP-IPV/Hib Acellular DTP-IPV Tdap	School-based programmes
France	2,3,4,16-18 mo	2,3,4,16-18 mo 11-13 yr (1998)	Wholecell DTP-IPV/Hib Tdap	A government-funded, national programme that is mainly delivered by private physicians (60% uptake)
Germany	2,3,4,11-14 mo	2,3,4,11-14 mo 14-16 yr	Acellular DTP-IPV/Hib-HBV Tdap	The booster dose is given in physicians' offices (uptake 20-30%)
Australia	2,4,6,18 mo 4 yr	2,4,6 mo 4 yr 15-17 yr	Acellular DTP-HBV or acellular DTP only Acellular DTP Tdap	The adolescent dose is provided by the government and is administered in schools
United States	2,4,6,18 mo 4-6 yr	2,4,6,18 mo 4-6 yr 11-12 yr	Acellular DTP or DTP-IPV	

3.4.5 Feasibility of implementation in the Netherlands

In order to assess the feasibility of implementation of adolescent pertussis vaccination in the Netherlands, it is important that the aim of vaccination is clearly stated. Either it is the intention to protect those infants who are too young to be fully immunized themselves, or vaccination is introduced to lower both incidence in the youngest infants and overall incidence. This is important, because the aim of the vaccination determines to a large extent which prevention strategy appears to be most attractive. If the aim of vaccination is to protect those young infants, maternal immunization and 'cocooning' (the vaccination of individuals around the newborn) should be taken into account as well. Then, the ethical aspects of vaccination of persons who do not directly benefit from the vaccination themselves are of importance.

Should pertussis vaccination of adolescents be attractive, it remains to be seen at what age this vaccine could be given. Halperin et al. (2005) described the experiences of Canada, France, Germany and Australia with implementation of their pertussis vaccine booster-dose programme in adolescents. In Table 3.1, these programmes are described. From the table, it can be seen that some countries used physicians, e.g. the general practitioner, as vaccination provider while other countries provide the vaccination in a school setting. The uptake in physician's settings was relatively low (20-60%), whereas no information was available on the uptake in school settings. In the Netherlands, infants are vaccinated in consultation offices by a physician specialized in early childhood. School children (9 years of age) are vaccinated by a school physician or they are invited to go to Municipal Health Centres. This appears to be a satisfying approach in terms of uptake of the Td vaccine and could possibly be an option for adolescent pertussis vaccination as well. One other option is to combine pertussis vaccination with another potential new vaccination in adolescence, like HPV vaccination (see section 3.5). A problem is that in the Netherlands, possibly only women will be regarded as a target group for HPV vaccination, so then men would be missed for the pertussis vaccination.

Humiston et al. (2005) concluded that adolescents have unique health care needs, and that there are some barriers to reach them. Some promising interventions for vaccination of

adolescents are outlined in this article. At the health care system level, reducing out-of pocket costs for adolescents by offering free vaccinations, expanding access to immunizations (convenient opening hours services or bringing services closer to the client), and implementing vaccination programmes in schools were effective. Halperin et al. (2005) also concluded that school-based programmes appeared to be most successful in achieving high rates of immunization. In the Netherlands, children in the age of 5, 9 and 14 years are invited for a preventive examination by a school physician. The latter visit (at the age of 14) could possibly be combined with pertussis booster vaccination. At present, no vaccination is given at that age. However, the most appropiate age at which vaccination should be given is dependent on the aim (reducing overall morbidity or reducing infant morbidity) and the expected effectiveness of vaccination at that age.

3.4.6 Summary

The main conclusion of this section is that pertussis vaccination of adolescents – aiming to prevent pertussis in both infants and adolescents – possibly could be cost-effective. However, conclusions should be interpreted with caution, because of great uncertainties in the estimates of the true incidence of pertussis morbidity, transmission routes and the extent of herd immunity. The cost-effectiveness ratios range from cost-saving to $187,081 per life year gained, depending on the level of herd immunity assumed. Converting this to 2005 Euros will result in a range from cost-saving to €186,000 per LYG. Nearly all the existing cost-effectiveness results appeared to be sensitive for the level of herd immunity and the degree of underreporting. From the health care perspective, herd immunity has to be at least 20% according to Caro et al. (2005a) and 60% according to Lee et al. (2005). Additional information about disease incidence, vaccine efficacy, and vaccine adverse events would contribute to a future policy decision about implementation of this vaccine.

Cost-effectiveness: *
Transferability: *
Implementation: *

3.5 Human papillomavirus vaccination of adolescents

3.5.1 Description of health problem

Cervical cancer is the second most common cancer among women worldwide, accounting for about 10% of all cancers (Franco and Harper, 2005). In 2003, 214 women died from cervical cancer in the Netherlands (CBS, 2005) and each year approximately 700 women are diagnosed with this disease (NKR, 2004). Cervical cancer is caused by a persistent human papillomavirus (HPV) infection (Franco and Harper, 2005). HPV comprises more than 100 different types of viruses; approximately 40 of these are specific for the ano-genitial region. Human papillomaviruses are the most common sexually transmitted viral agents. The prevalence of HPV infection in the population therefore peaks among persons in their late teens or early twenties during the years following onset of sexual activity (Jacobs et al., 2000). Therefore, 20 to 25% of young women are infected with HPV. Most of the HPV infections are transient, but the persistent infections, however, might lead to cervical cancer. HPV types 6 and 11 may cause genital warts and HPV types 16 and 18 are associated with cervical cancer (Sanders and Taira, 2003). The period between the start of the infection and the development of cervical cancer is quite large (>20 years) (Bonnez et al., 2002).

3.5.2 Description of intervention and current situation in the Netherlands

The intervention in this section concerns vaccination against human papillomavirus infection in adolescents that are not yet sexually active[1]. Such vaccination is expected to have a positive influence on the future incidence of cervical cancer (Koutsky et al., 2006). A screening programme will always be necessary because a quarter of the cervical intraepithelial neoplasia (CIN-3, pre-cancerous lesions of the cervix) and cervical cancers cases are caused by other HPV genotypes. At present, it is uncertain whether boys should be vaccinated as well. Including boys in a vaccination programme is expected to limit the spread of disease (herd immunity) and will probably lead to a further decrease in overall incidence of cervical cancer (Taira et al., 2004).

At present, all Dutch women between the ages of 30 and 60 years are screened for cervical cancer every 5 years. Consequently, a large reduction in progressed forms of cervical cancers was achieved (Van Ballegooijen et al., 1992). A major problem with the current screening programme is the difficulty in recognizing the pre-stage cervical cancers that will develop into progressed stages, as many pre-stage cervical cancers show spontaneous regression (Crum, 2002). Furthermore, the current screening tests lack sensitivity and are relatively expensive. Often screening will unnecessary frighten women because the detected abnormal result would never have progressed to cancer (Quint et al., 2006). Furthermore, as the screening programme is a form of secondary prevention, it has little impact on circulation and transmission of the virus in the population.

Two vaccines against HPV were developed: Gardasil® and Cervarix®. Gardasil® has recently obtained a European licence (September 2006). A decision on the licensure of Cervarix® is expected in the first half year 2007 (Boot et al., 2006). The effectiveness of these vaccines in the prevention of cervical cancers is high: 90% effectiveness against transient HPV16/18 infections and almost 100% protection against persistent infections (minimal 6 months infected with HPV 16/18) (Villa et al., 2006). Koutsky et al. (2006) showed in their trial 100% efficacy of an HPV vaccine over an 18-month period in preventing persistent HPV 16 infection and HPV 16-specific CIN. Long term effectiveness (>5 years) is still uncertain.

3.5.3 Results from economic evaluation studies

The literature search resulted in six cost-effectiveness studies of HPV vaccination (Appendix 6, Table 6.5). Four of the six studies were of good quality and are described in this subsection. All four studies were performed in the United States. The first study compared HPV-16 and 18 vaccination of girls at age 12 (in three doses) and a booster at 22 years with no vaccination intervention. This resulted in a cost-effectiveness ratio of $ 14,583 per QALY. Including vaccination of boys appeared not to be cost-effective (Taira et al., 2004).
The second study compared several combination strategies of vaccination and screening varying the screening intervals and starting ages of screening (Goldie et al., 2004). As this study models several combinations of the screening programme and vaccination, this study can be used to receive an impression which strategy would be most cost-effective.
In Table 6.5 (Appendix 6) only the most cost-effective strategies are shown. The most cost-effective strategy was then screening (HPV test inclusive) starting at age 35 every 5 years and vaccination (100% efficacy) at 12 years, with a ratio of US$ 12,300/QALY. Other strategies in this study had ratios varying from US$ 17,200/QALY (screening starting at age 30 every 5

[1] See De Melker HE, Gerritsen AAM, Hahné SJM (Eds.) for further discussion on this subject.

years and vaccination (90% efficacy)) to US$ 3,867,500/QALY (screening (liquid-based) starting at age 18 every year and vaccination (90% efficacy)). The third study compared (school-based) HPV vaccination of females aged 12 years and standard care with standard care only (=conventional, biennial, cervical cancer screening starting at age 16 years) (Sanders et al., 2003). This resulted in a cost-effectiveness ratio of $ 22,755 per QALY. HPV vaccination appeared to be more cost-effective if no boosters but lifetime immunization was assumed, if the incidence of HPV infection was higher and if the screening frequency was decreased to every five years. The fourth study examined 40 strategies, varying from screening only strategies (conducted every 1, 2, 3 and 5 years) to strategies combining screening plus vaccination at identical intervals, varying the ages of screening onset (ages 18 years, 22 years, 24 years, 26 years, and 30 years) (Kulasingam and Myers, 2003). The screening only interventions with less frequent intervals and later starting ages were cost-effective, with ratios of $ 21,912/LYG at a maximum. The combination strategies with vaccination were less cost-effective, with ranges from $ 44,889 per LYG (for vaccination and screening every 2 years, starting age 24 years compared with screening every 3 years) to $ 236,250 per QALY (vaccination and screening every year starting at age 18 compared with the same strategy starting age 22 years.

Of the studies mentioned above, only Taira et al. (2004) included herd immunity effects by using a transmission model. Vaccine evaluations that do not include disease transmission can underestimate actual vaccine benefit (Brisson and Edmunds, 2003; Edmunds et al., 1999). So the other results could be underestimated. Dasbach et al. (2006) reviewed the state of mathematical modelling of HPV disease for evaluating HPV vaccination strategies, including the four above mentioned studies. A consistent finding was that vaccinating females may be cost-effective. The cost-effectiveness of vaccination further improved if vaccination was used to delay the start of or widen the interval between consecutive cervical cancer screening intervals. The most important determinants that influence cost-effectiveness of vaccination are: the duration of vaccine protection, vaccine effectiveness, vaccination cost, the health utilities used to estimate QALYs and whether or not males were vaccinated (Dasbach et al., 2006).

In 2006, a preliminary cost-effectiveness analysis is performed by the Dutch Institute of Public Health and the Environment (RIVM) and VU University Medical Center as part of an assessment study on the introduction of universal HPV vaccination of pre-adolescent girls (Boot et al., 2006). They used a rather conservative approach in their analysis. Although first results with regard to cost-effectiveness are promising, the analysis at present cannot be used to underpin major decision making on the future implementation of HPV vaccination in the Netherlands

3.5.4 Transferability of foreign study results to Dutch context

The screening programme in the US is entirely different from that in the Netherlands. In the US, the starting age of screening is earlier (21 years) and the interval between subsequent invitations is only two years. In the Netherlands, women are entering the screening programme at the age of 30 years with an 5-year interval, with a participation rate of about 70%. The Dutch screening programme is more cost-effective than the US screening programme (Van den Akker-Van Marle et al., 2002). A conclusion as stated in most of the cost-effectiveness studies as described above is that HPV vaccination would become more favourable in combination with a simultaneous change of the current screening programme, namely to start at a later age and use wider intervals between consecutive screenings. In

comparison to the US situation, the adaptations to the cervical cancer screening programme are already practised in the Netherlands. Uncertainties surrounding vaccine effectiveness will be of major influence on the cost-effectiveness of HPV vaccination in the Netherlands. Taira et al. (2004) examined the influence of broadening the screening intervals on the cost-effectiveness of a vaccination programme. They concluded that the wider the screening interval is (>every 2 years), the more cost-effective the vaccination programme is expected to be.

The US does not have a national immunization programme like the Netherlands has. Probably, a lower vaccine price is achievable in the Netherlands than in the US because of high vaccine volumes needed in the context of a national immunization programme. Furthermore, the vaccination coverage rate in the US is in general lower than in the Netherlands. The US cost-effectiveness studies vary the coverage rate between 50 and 100%. In the Netherlands vaccination coverage is traditionally very high (>95%) for childhood vaccination (<9 years). However, at present it is unknown whether the coverage rate would be as high in adolescents as achieved in childhood. Recently, a catch-up programme with a Meningococcal-C vaccine was performed among 10 to 12 year old adolescents and the coverage rate in this age-group appeared to be high as well (Boot et al., 2006). It is not known whether the uptake of HPV vaccination with a similar catch-up programme would be comparable.

3.5.5 Feasibility of implementation in the Netherlands

Whether vaccination against HPV is implementable in the Netherlands may be influenced by several factors. First of all, the vaccine price is not yet known. This can highly influence the cost-effectiveness of vaccination. The preliminary Dutch study used threshold analysis to estimate at what vaccine price HPV vaccination becomes borderline cost-effective. They showed that the vaccine price should not be higher as € 95 per vaccine dose (Boot et al., 2006). However, as this is a preliminary analysis, these results should be interpreted with caution.

Resistance to a vaccine may arise because HPV is a sexually transmitted disease (McNeil, 1997; Garnett and Waddell, 2000). Zimet (2005), on the other hand suggests that an HPV vaccine may be reasonably accepted. It will be very important to inform the general population about the relation between HPV-infection and cervical cancer (Quint et al., 2006). The introduction of an immunization programme against the two most prominent high-risk HPV types could make women think they are completely protected. Consequently, participation in the screening programme might reduce and the incidence of cervical cancer due to non HPV-vaccine types might increase. Education again is very important in this matter (Quint et al., 2006). At present, adolescents do not yet receive any other vaccination. Hence, no infrastructure for vaccination of adolescents exists. According to some Dutch experts, the best way to implement the HPV vaccination among adolescent girls is by inviting them to a Municipal Health Centre. One other possibility would be that the vaccination is provided by a school physician. In both situations, problems might arise with regard to informed consent, as this is needed from the parents.

One option to increase the participation rate could be the combination of HPV vaccination with potential other future adolescent vaccines, such as hepatitis B vaccination (see Section 3.2). Another option could be the integration of the HPV vaccination in the DTP and BMR vaccination in 9 year old children. In the US vaccination for HPV is already

recommended for 9 to 25 year old women. In Europe the HPV vaccine (Gardasil®) has also been licensed for men, although efficacy data on male HPV vaccination are lacking at present. New cervical cancer screening technologies are developed, and the ability to test for high-risk types of HPV DNA is refined (Vijgen et al., 2005). In this context, it is important to study all possibilities for prevention of cervical cancer in an integral way. All possible combinations of vaccination and screening should be studied in order to find the most effective and efficient prevention strategy.

3.5.6 Summary

HPV vaccination of female pre-adolescents is possibly cost-effective. Not all interventions as found in the studies appeared to be cost-effective. The cost-effectiveness ratios of the interventions that were cost-effective range from US$ 12,300/QALY to US$ 24,300/QALY, depending on assumptions made. Converted to 2005 Euros, the ratios will range from € 12,225 to € 24,152 per QALY gained. Nearly all the existing cost-effectiveness results appeared to be sensitive to the age at which vaccination is given, vaccine efficacy, vaccine price and duration of protection. More research is needed on those factors, as well as on the cost-effectiveness of HPV vaccination in men. The impact of the vaccination on the frequency of screening is important. Based on currently available (international) data it can be concluded that universal HPV-vaccination of pre-adolescent girls in the Netherlands will only be cost-effective under certain base case assumptions (Boot et al., 2006). The feasibility of implementation of HPV vaccination in the Netherlands depends among others on the price of the vaccine and the knowledge of parents and adolescents about the importance of vaccination and screening. Furthermore, it is important to find the best way of providing the vaccine to adolescents in optimalizing the compliance among them.

Cost-effectiveness *
Transferability *
Implementation *

4. Results: improving evidence on cost-effectiveness of interventions from the 2003 report

4.1 Introduction

Of the 18 interventions that were listed in the 2003 report (Dirkmaat et al., 2003), eight interventions either were implemented, have found their way into (clinical) guidelines, or will be implemented in the near future. The cost-effective preventive interventions that were implemented are (parts of) the National Immunization Programme, influenza vaccination of elderly, needle exchange programmes, PKU/CHT screening and syphilis screening of pregnant women. Two diabetes related interventions have found their way into clinical guidelines for the treatment of diabetes. One intervention, chlamydia screening, will possibly be implemented on a national scale in the next few years. For the remaining ten interventions, a literature review was carried out to improve the rather random evidence that was presented in the 2003 report. Herefore, we have used methods similar to those used for the interventions that were described in chapter 3 of this report (see section 2.2 for methods used).

Using the more strict criteria, four interventions that were listed in the 2003 report had to be removed from the list of promising interventions. For two interventions it was not possible to identify three or more good-quality economic evaluations. These interventions were the reduction of intake of saturated fats to reduce the incidence of heart disease and the promotion of breastfeeding. Two interventions could not be updated for the present report because the intervention itself showed a large diversity in the way it was operationalized, as was the case with interventions to prevent falls of elderly people and with hepatitis A vaccination of certain groups of employees. Details on the reason why interventions from the 2003 report were excluded in the current report can be found in Appendix 2.

In the remainder of this chapter, update information is presented for the remaining six intervention from the 2003 report. The information is structured in a similar way as in chapter 3.

4.2 Fluoridation of drinking water

4.2.1 Description of the health problem

Dental decay (caries) is a very common disease as almost every adult individual has one or more dental cavities, and 45% of the 5 year old children in the Netherlands have caries already in their milk teeth (Kalsbeek, 2002). Caries is not only associated with dental pain and the risk of tooth loss, but has a broader impact on one's health (problems with chewing, stomach complaints). The number of decayed, missing, or filled teeth (DMFT-index) is used as a measure for caries experience. Because filled and missing teeth are included in this index, it represents the accumulated caries experience, rather than the actual caries prevalence. Caries is related to socioeconomic status: for instance, children of lower educated mothers have more caries as compared to children of higher educated mothers (Kalsbeek and Poorterman, 2003). In the Netherlands, dental caries has dramatically decreased during past

decades and has stabilized since 1990 (Kalsbeek and Poorterman, 2003). Currently, children of 12 years of age have a mean DMFT-index of less than one (0.8) (European HFA Database, 2006). This caries reduction is attributable to the improvement of tooth brushing behaviour in general, as well as to the widespread use of fluoride (e.g. fluoridated toothpaste). Nevertheless, the caries problem in our country is still far from being solved (Kalsbeek and Poorterman, 2003). This also appears from the cost of illness figures for caries: treatment of dental caries results in total costs of € 1.6 billion (Slobbe et al., 2006).

4.2.2 Description of the intervention and the current situation in the Netherlands

Fluoride decreases the acid-solubility of the teeth, which makes the teeth stronger. So, prevention of dental decay can be realized by exposing the teeth to fluoride. Different strategies to enhance fluoride levels include fluoridated toothpastes, fluoride mouth rinses and gels, and fluoridated drinking water. The latter strategy is implemented in many areas of the United States, and such community water fluoridation programmes (CWFP) were proven to be very effective (Truman et al., 2001). Water fluoridation even appears on the CDCs (Center for Disease Control and Prevention) list of ten great public health achievements (together with e.g. immunizations, safer and healthier foods, et cetera.) (http://www.cdc.gov/mmwr/preview/mmwrhtml/00056796.htm). McDonagh et al. (2000) found that water fluoridation was associated with an increase of almost 15% in the proportion of children without caries, and a DMFT reduction of 2.25. Moreover, the evidence suggests that water fluoridation has a beneficial effect over and above that of fluoridated toothpaste (and other sources of fluoride) (McDonagh et al., 2000). According to McDonagh and colleagues, there is some evidence that water fluoridation reduces sociodemographic inequalities. McDonagh et al. (2000) also investigated the possible negative effects. There was only one statistically significant negative effect of fluoridation: dental fluorosis (ranging from some white spots on the teeth, to brown coloration of the teeth). A dose-response relationship was identified, with a prevalence for fluorosis of aesthetic concern of 12.5% at a fluoride level of 1 ppm (McDonagh et al., 2000). During the 1960s and 1970s the drinking water in the Netherlands was fluoridated. Due to societal resistance the underlying law was not extended in 1976. So, currently, in the Netherlands the water is not fluoridated. As in other countries, almost all toothpastes are fluoridated nowadays.

4.2.3 Results from economic evaluation studies

Four studies that evaluated the costs and benefits of drinking water fluoridation were included (Appendix 7, Table 7.1). All studies concluded that CWFPs are cost-saving.

The most recent study was performed by O'Connell et al. (2005). This study estimated the net costs of a CWFP by comparing the programme costs with the treatment savings associated with prevented tooth decay. It was assumed that a CWFP was implemented if the difference between natural fluoride concentration of water and recommended fluoride concentration (CDC-recommendation varies between 0.7 and 1.2 ppm) was at least 0.3 ppm. It was assumed that the adverse effects of exposure to water fluoridation were negligible. Furthermore, productivity losses due to morbidity were not included. The authors conclude that CWFPs were associated with net savings (BCR 22:1 to 135:1). The net savings were most sensitive to changes in CWFP effectiveness and the decay increment in nonfluoridated areas. Nevertheless, all variations in the sensitivity analysis resulted in net savings. One of the comments of the authors is that the savings due to CWFP are reduced as use of other fluoride recources (e.g. fluoridated toothpaste) increases. Griffin et al. (2001) also calculated

the net savings of water fluoridation as the costs of water fluoridation minus the savings from averted tooth decay. They included only benefits for people between 5 and 65 years of age, and neglected any adverse effects of fluoridation. The authors found that water fluoridation was cost-saving, and that their findings were very robust to variations in parameters. Community water fluoridation was still cost-saving under worst case scenarios (except for very small communities (fewer than 5,000 people)). Wright et al. (2001) focussed on the minimum population size for which oral health benefits from water fluoridation would be greater than the costs of that fluoridation programme. Net savings were calculated. Due to the absence of data, the effectiveness of fluoridation was limited to people less than 35 years of age. Fluoridation appeared to be cost-saving for communities of 1,000 people and above, especially in communities with a high proportion of children or a low socioeconomic status. Birch (1990) evaluated the costs of water fluoridation in relation to its effect on caries. They concluded that water fluoridation would cost £ 1.60-19.46 per reduced DMFT person year. All assumptions in this analysis were biased against fluoridation, so the findings probably are underestimating the actual cost-effectiveness of water fluoridation.

4.2.4 Transferability of foreign study results to Dutch context

Systematic reviews and economic evaluations conclude that water fluoridation is safe, effective, and cost-effective. The conclusion of the cost-effectiveness studies that water fluoridation is cost-effective is anticipated to be transferable to the Netherlands, but not without adjustments for the Dutch situation. In the country, water fluoridation would prevent a substantial proportion of the burden of disease caused by dental caries, and of the costs of dental caries, which are estimated at € 1.6 billion in the Netherlands (Slobbe et al., 2006). Nevertheless, over the last decades caries prevalence declined, largely attributed to the widespread use of fluoridated toothpaste. Since the (cost-)effectiveness of fluoridation depends inter alia on caries incidence, the question may be raised whether water fluoridation would still be (cost-)effective nowadays. However, even the most recent economic evaluation shows that the additional protective effect of fluoridated drinking water is still significant (notwithstanding the use of fluoridated toothpaste).

Furthermore, cost-effectiveness also appeared to be dependent on the natural fluoride concentration of drinking water in the area. This natural concentration is very low in the Netherlands (<0.3 ppm (Versteegh, 2005)), which would have a positive effect on the cost-effectiveness of the fluoridation of drinking water in our country.

4.2.5 Feasibility of implementation in the Netherlands

The implementation of fluoridation of drinking water is practically feasible, by adding a controlled dose of a fluoride compound to the drinking water. This could be realized at relatively low cost. On the other hand, there are also several major barriers for implementation. In the first place, at present the addition of chemicals to drinking water is prohibited by law in the Netherlands. This law came into effect because it was widely perceived that drinking water should not be used as a vehicle for pharmaceuticals. Furthermore, fluoridation of drinking water would conflict with the freedom to choose for natural drinking water. This principle of freedom of choice is considered as an important basic principle in the Netherlands.

4.2.6 Summary

Fluoridation of drinking water in the Netherlands would probably be cost-saving as the costs of fluoridation will be outweighed by the savings due to reduction of caries. However, people would also run the risk of fluorosis (of aesthetic concern). Although practically feasible, the many objections against fluoridation of drinking water make its implementation rather improbable.

Cost-effectiveness: **
Transferability: *
Implementation: *

4.3 Folic acid fortification of staple foods

4.3.1 Description of the health problem

In the Netherlands, it is estimated that 2.4% of all liveborn babies have a major congenital abnormality demanding medical care during the first year of life (EUROCAT, 2005). One of the most common congenital disorders is a neural tube defect (NTD). A NTD results from a failure of closure of the neural tube during early embryogenesis. The two most frequent NTDs are anencephaly and spina bifida (Northrup and Volcik, 2000). Anencephaly is a lethal condition, and the viability of infants with spina bifida is determined by the type of lesion. The symptoms of spina bifida vary from very mild symptoms to incontinence, paralysis, and hydrocephalus. The total birth prevalence (i.e. including live births, stillbirths and induced abortions) of NTD in Europe is about 1 in 1000 (EUROCAT, 2000; Cornel, 2003).

4.3.2 Description of the intervention and the current situation in the Netherlands

Folate is needed to replicate DNA, and for the production and maintenance of new cells. This is especially important during periods of rapid cell division and growth such as pregnancy. Folate deficiency hinders DNA synthesis and cell division. Improving the folate status in pregnant women was proven to reduce the risk of NTDs (MRC, 1991). An adequate folate status, achieved by the intake of synthetic folic acid, can result in the prevention of more than two thirds of all NTDs (MRC, 1991). Several strategies to reach an adequate folate status for effective prevention of these birth defects exist. These include promotion of the use of oral folic acid supplements several weeks before and after conception, and mandatory folic acid fortification of staple foods. Most European countries (including the Netherlands) have adopted the former strategy (Busby et al., 2005). In the northern provinces of the Netherlands a reduction in NTD prevalence in 2000-2002 was shown as compared to 1989-1991 (Busby et al., 2005). Moreover, a Dutch study found that the cost-effectiveness of this current strategy was €1800 in the base case and remained below € 4500 in the sensitivity analysis (Postma et al., 2002). However, in Europe the supplementation strategy has not led to a substantial decline in the prevalence of NTDs (Busby et al., 2005). This suggests that a policy of recommending periconceptional folic acid supplementation may not be very effective. In other countries (e.g. US, Canada, Chili, et cetera) the strategy of mandatory folic acid fortification was implemented. In these countries, the blood folate status has improved following the fortification of flour with folic acid, and NTD rates fell by 19-78% (Eichholzer et al., 2006).

4.3.3 Results from economic evaluation studies

Three studies were found that investigated the cost-effectiveness of mandatory folic acid fortification of staple foods for the prevention of NTDs (Appendix 7, Table 7.2). All studies were performed in the US, and they all concluded that folic acid fortification is cost-saving.

Grosse et al. (2005) performed an ex post economic evaluation of mandatory folic acid fortification of cereal grain products. The fortification strategy was found to be cost-saving, even in the worst case scenario. Fortification costs $ 3 million per year in the US, and the averted NTDs result in a total societal benefit of $ 312 to $ 425 million, and in a savings of $88 to $146 million on direct medical costs. Kelly et al. (1996) calculated the cost-effectiveness of both the supplementation strategy and several fortification strategies (ranging from 140 to 700 mcg folic acid per 100 g grain). Fortification, at all levels investigated, resulted in overall cost-savings as well as in gains in QALYs. The supplementation strategy gained more QALYs than fortification at 140 mcg of folic acid, but it would cost more than any of the fortification strategies. Fortification with 700 mcg folic acid per 100 g grain would result in cost-savings of about $ 13,000 ($ 7000 - $ 14,000) per QALY gained. Romano et al. (1995) compared the economic costs and benefits of fortifying grain with folic acid to prevent NTDs. By averting costly birth defects, fortification would be expected to yield net economic benefits. The best estimate of the benefit to cost ratio is 4.3:1 for low-level fortification (140 mcg/100 g) or 6.1:1 for high-level fortification (350 mcg folic acid per 100 g grain). In the US these strategies would result in a net economic benefit of $ 94 or $ 252 million, respectively. The costs per case averted would be $ 92,000 for the low-level strategy and $ 65,000 for the high-level strategy. This study also included the estimation of the cost-effectiveness of the voluntary use of folic acid supplements. This strategy would result in $ 132,000 per NTD case averted. Hence, in this study fortification was found to be more cost-effective than supplementation. No cost-effectiveness study on the combination of fortification and supplementation was found.

4.3.4 Transferability of foreign study results to Dutch context

Since folic acid fortification of staple foods is a relatively cheap intervention, and the benefits in terms of savings due to prevented NTD cases outweigh the costs of fortification, all studies concluded that mandatory folic acid fortification would be cost-saving.
However, the studies only evaluated the effect of folic acid fortification on the birth prevalence of neural tube defects. They ignored the increasing evidence about other - both beneficial and adverse - effects of folic acid. Recent studies suggest that folic acid has diverse health effects in individuals (Kloosterman et al., 2006; Verhoef and Katan, 2006; Cornel et al., 2005; Van Amsterdam et al., 2004). These studies report the following positive effects: prevention of other birth defects, improved fertility, prevention of (recurrence of) cardiovascular disease, prevention of some cancers, prevention of cognitive decline and dementia, and prevention of anemia. The reported negative effects are: increased cancer risk (at high levels of folic acid), masking of vitamin-B_{12} deficiency, and promotion of tumor progression. Although there is much uncertainty about some of these supposed effects, others are more evidence based and should be taken into account in current economic evaluations of food fortification. Inclusion of the potential adverse effects of folic acid might result in lower cost-effectiveness estimates as compared to the abovementioned studies that only included the preventive effect of folic acid on NTDs (the economic evaluations only included the risk of masking a vitamin-B_{12} deficiency). On the other hand, inclusion of the other favourable effects could lead to even larger benefits. Therefore, the results of the described economic evaluations should be considered as incomplete to fully assess the cost-effectiveness of

fortification and supplementation, given the rapidly increasing knowledge on all effects of folic acid. It seems that the beneficial effects of folic acid (e.g. prevention of NTDs), should be balanced against adverse effects of folic acid (e.g. promotion of cancer). An assessment of the current evidence for all related diseases is needed before a risk-benefit analysis for all potential effects can be performed. Currently, quantitative risk benefit assessment methodologies are under development at the RIVM.

4.3.5 Feasibility of implementation in the Netherlands

The current policy in the Netherlands implies the promotion of periconceptional use of folic acid supplements. Although this is a cost-effective strategy in the Netherlands (€ 1800/life year gained) (Postma et al., 2002), folic acid fortification of foods may be cost-saving and more effective (i.e. leading to a larger reduction of the prevalence of NTDs). At present in the Netherlands, about two thirds of the target group uses supplements, but only one third uses it the entire advised period (Cornel, 2002; Meijer and De Walle, 2005). Contrary, mandatory food fortification would increase the folate status of every woman of childbearing age. Concurrently, the exposure of non-target groups (e.g. men) in the population will become higher. Besides, since the use of folic acid supplements is lower among women of lower socioeducational status (Busby et al., 2005), mandatory food fortification might decrease socioeconomic inequalities in NTD prevalence (Eichholzer et al., 2006).

Technically, the implementation of folic acid fortification of grains is not a problem. However, there are several objections against such a mandatory food fortification. These include the above mentioned possible health risks related to raising the folate status of the total population. Furthermore, it is suggested that there is a lack of recognition of the public health importance of NTDs. This may be related to the fact that the great majority of NTDs pregnancies are now terminated in many European countries, rendering them invisible to all but the affected families (EUROCAT, 2005). Finally, mandatory food fortification raises the issue of autonomy and freedom of choice (Cornel, 2005). Mandatory fortification of flour can be limited to part of the products, which can be labeled, so that the possibility to decide to eat unfortified foods remains. In the US, whole wheat flour is not fortified for this reason.

4.3.6 Summary

The results of the cost-effectiveness analyses suggest that mandatory folic acid fortification of staple foods would be cost-saving with regard to the prevention of NTDs. However, recent evidence on other favourable and harmful effects of folic acid was not included in the economic evaluations. Further research is needed to gain more insight into the diverse effects of folic acid. Such a risk-benefit analysis should be the basis of future comprehensive economic evaluations of mandatory folic acid fortification and supplementation.

Cost-effectiveness: **
Transferability: *
Implementation: *

4.4 Vaccination against varicella zoster virus

4.4.1 Description of the health problem

Varicella zoster virus (VZV) is one of the most infectious viruses; 80-90% of exposed seronegative persons will develop varicella disease (chickenpox). In the Netherlands, 49% of

2-years-old children have had chickenpox. This seroprevalence increases to 93% for 5-years-olds, and 98% for those over 6 years of age (De Melker et al., 2006). The vast majority of the cases occurs during childhood and has only mild symptoms: fever and generalized pruritic rash. The most frequent complication is bacterial superinfection of the skin, lungs or bones. In individuals with decreased immunity, chickenpox may have a more severe course with serious morbidity and even mortality. Moreover, pregnant women who develop varicella have a 2% risk that the baby will be affected with congenital varicella syndrome (abnormalities, mental retardation). Reactivation of the latent infection of VZV established during a childhood chickenpox infection can cause shingles later in life. Chickenpox causes about 40,000 GP consultations, 200 hospital admissions, and 2.3 deaths each year (De Melker et al., 2006). So, although VZV infections are generally mild and self-limiting, due to their high incidence among children they give rise to considerable morbidity and, occasionally, mortality.

4.4.2 Description of the intervention and the current situation in the Netherlands

Prevention of chickenpox is possible by means of vaccination against VZV[1]. The Oka-vaccine is currently available as a single-component vaccine, and clinical studies show that vaccine efficacy is 70-100% (Boot et al., 2006). Recently, the vaccine is registered in many European countries, including the Netherlands. Currently, VZV vaccination is not included in the National Immunization Programme (NIP). The effectiveness of varicella vaccination decreases over time from 97% in the first year to 84% in the years 2-8 (Vazquez et al., 2004). The frequency of breakthrough infections will be reduced after a two-dose schedule. However, a second varicella vaccination after 1-3 months would require an adaptation of the NIP, since the second MMR-vaccination (Measles, Mumps and Rubella) is given at 9 years of age (Boot et al., 2006).

4.4.3 Results from economic evaluation studies

Many economic evaluations of universal childhood varicella vaccination programmes were performed. A study of Thiry et al. (2003) reviewed cost-effectiveness analyses up to the end of 2002. Below, the results of this review, as well as the results of five individual economic evaluations that were performed after 2002, are summarized (Appendix 7, Table 7.3).

With regard to universal vaccination of children, Thiry et al. (2003) concluded that, in spite of the diversity in assumptions, all included studies point in the same direction: compared to no vaccination, universal varicella vaccination would generate indirect savings to society (mean benefit to cost ratio of about 4:1). This conclusion was sensitive to the vaccine price and the value assigned to productivity losses of parents. According to Thiry and colleagues, vaccination would not generate savings from the healthcare payer's perspective.

The study by Hsu et al. (2003) also reported cost-savings from the societal perspective, but not from the health care payer's perspective. Recent studies of Coudeville et al. (2004 and 2005), Ginsberg and Somekh (2004), and Banz et al. (2003), in Italy, France and Germany, Israel, and Germany, respectively, reported that universal childhood varicella vaccination would be cost-saving from both perspectives (although considerably less cost-savings from the healthcare payer's perspective were reported). This difference between the two perspectives is related to the productivity losses associated with parents' absence from work

[1] See De Melker HE, Gerritsen AAM, Hahné SJM (Eds.) for further discussion on this subject.

while caring for their sick children. These costs are generally only included in the societal perspective, and not in the healthcare payer's perspective. Brisson et al. (2003) was the only included study that reported a loss of QALYs due to the vaccination. While all other studies assumed that childhood vaccination does not influence the epidemiology of zoster (shingles), Brisson et al., assumed that varicella vaccination would increase this incidence. Since zoster is a more severe disease, having larger QALY losses than varicella, a small increase could wipe out QALY gains from varicella reductions. Hence, this study did not support the cost-effectiveness of varicella vaccination.

4.4.4 Transferability of foreign study results to Dutch context

A major point of uncertainty in the assessment of the cost-effectiveness of universal varicella vaccination is the potential effect of vaccination on the incidence of zoster later in life (Boot et al., 2006). It is suggested that a decrease in chickenpox incidence will cause a temporal increase of the incidence of shingles (Brisson et al., 2003; Goldman, 2005). If this rise in zoster incidence will occur, varicella vaccination will not be cost-effective for the first 50 years. However, there is no consensus concerning this anticipated zoster increase (Hammerschmidt et al., 2004; Jumaan et al., 2005). So, as long as there is uncertainty about the effect on zoster epidemiology, definite conclusions about the cost-effectiveness of varicella vaccination can not be drawn. Furthermore, the morbidity of chickenpox increases with age (Boot et al., 2006). In the Netherlands, the mean age of seroconversion is relatively low, and thus, the burden of disease caused by varicella is relatively low. The GP consultations and hospital admissions for chickenpox are lower than in other European countries (Boot et al., 2006). This lower burden of disease (less severe cases) will make varicella vaccination in the Netherlands less cost-effective in comparison with other countries. To check whether or not the burden of disease figures are an underestimation, the RIVM is currently collecting data about the actual incidence of complications due to chickenpox.

4.4.5 Feasibility of implementation in the Netherlands

All studies evaluated the cost-effectiveness of one separate vaccination, while currently a tetravalent MMRV vaccine is available. In the future, the MMR vaccine in the NIP could be replaced by a MMRV vaccine. The use of such a combination vaccine could have a positive effect on the coverage rate of varicella vaccination. On the other hand, a recent study found that only 22% of the parents reported that they would have their children vaccinated against chickenpox (Van de Bovenkamp-Meijer and Rümke, 2005). Dutch parents seem to perceive chickenpox as a benign, mild disease. Inclusion of vaccination for a disease that is perceived as a mild disease could have an effect on the uptake of other vaccinations within the NIP as well. Such an effect should be taken into account while considering the introduction of universal varicella vaccination. Furthermore, a second vaccination in the second live-year will prevent frequent breakthrough infections (Boot et al., 2006). However, such a second vaccination is not easily implementable in the current NIP, as the second MMR vaccination at present is given at 9 years of age (Boot et al., 2006).

4.4.6 Summary

In conclusion, universal childhood varicella vaccination could prevent most morbidity and mortality due to chickenpox. Based on international literature, it is expected that the introduction of varicella vaccination in the NIP could be cost-effective from a healthcare payer perspective and possibly even cost-saving from a societal perspective. Nevertheless,

the actual cost-effectiveness depends on several aspects that are still uncertain at the moment. These factors include the actual burden of disease caused by chickenpox in the Netherlands, the effect of varicella vaccination on zoster incidence, and on MMR coverage. Furthermore, a second varicella vaccination to prevent frequent breakthrough infections requires major changes in the NIP.

Cost-effectiveness: **
Transferability: *
Implementation: *

4.5 Stop smoking interventions

4.5.1 Description of the health problem

Smoking increases the risk of many diseases, such as lung cancer, COPD, and cardiovascular diseases. In the Netherlands, smoking is the risk factor with the highest burden of disease, being related to about 13% of the total amount of DALYs (De Hollander et al., 2006). About 30% of coronary heart disease mortality and about 14% of stroke mortality is caused by smoking. Approximately 11% of stomach cancer cases is caused by smoking (Trédaniel et al., 1997). Furthermore, 3.7% of the total costs of illness are attributable to smoking (De Hollander et al., 2006). In the Netherlands, 28% of the population smoked in 2005 (Willemsen, 2005).

4.5.2 Description of the intervention and current situation in the Netherlands

Tobacco control potentially decreases the burden of disease substantially. Tobacco control policy aims at reducing the number of smokers, either by increasing smoking cessation or by decreasing the initiation of smoking. This section, focuses on cessation of smoking in adults, because most evidence exists in this field (Feenstra et al., 2005a). For many smokers, it is hard to quit smoking on will power alone. Only 3-7% of the smokers who attempt to stop smoking on will power are still abstinent after one year (Zhu et al., 2000; Willemsen et al., 2003). A wide range of policy measures and therapies is targeted at the increase of this rate. Two types of interventions can be distinguished, the individual ones (i.e. self-help manuals, intensive counselling combined with pharmaceutical therapies) and the ones on population level (such as price increases by taxation, media campaigns and regulation) (Feenstra et al., 2005a).
Since the report of Dirkmaat et al. (2003) focused mainly on individual interventions from which GP counselling appeared to be most cost-effective, this section focuses on GP counselling as well. GP counselling can be provided in a minimal way (often called minimal counselling or ‘Kort stopadvies’ in Dutch) or in a more intensive way (often called structured GP counselling or ‘H-MIS’ in Dutch). Minimal counselling means short counselling by a GP or assistant in one consult that is not necessarily aimed to stop smoking or associated with smoking related diseases. Structured GP counselling implies counselling in one or two consults following a protocol (Feenstra et al., 2005a). GP counselling can be combined with either nicotine replacement therapy (NRT) with patches or gum or with Bupropion, which is medication to support a person who wants to quit smoking.

4.5.3 Results of economic evaluations

Five economic evaluation studies on smoking cessation (Appendix 7, Table 7.4) were included. One of the five studies took place in the Netherlands (Feenstra et al., 2005b). A more recent version of this study, which took account of health care costs for substitute diseases and relapse of quitters also more than one year after cessation (Feenstra et al., 2005a) is used.

Feenstra et al. (2005a) performed a cost-effectiveness study in which the cost-effectiveness of implementing several tobacco cessation interventions in the Netherlands was estimated. Minimal counselling and structured GP counselling appeared to be the most cost-effective individual interventions, with ratios of respectively € 9,100 and € 8,800 per QALY gained. When nicotine replacement therapy was added to the GP counselling the ratio was € 13,400 per QALY gained. No combination of GP counselling with Bupropion was included in this study because insufficient evidence on effectiveness (12 months sustained abstinence) was found for that combination. The ratios are conservative estimates because all future health care costs are included, including the savings from a reduced incidence of smoking related diseases and the extra health care costs for substitute diseases in longer life.
Cornuz et al. (2006) studied the cost-effectiveness of GP counselling and several nicotine replacement therapies (gum, patch, inhaler and spray) in six countries (Canada, France, Spain, Switzerland, United Kingdom and United States) for men and women separately. The ratios varied from $ 1,758 per LYG for men in Spain (patch) to $ 8,700 per LYG for women in France (inhaler).
In another study by Cornuz et al. (2003) the cost-effectiveness ratios were determined for pharmacotherapy (nicotine replacement therapy or Bupropion) compared to GP counselling in Switzerland. The cost per LYS for counselling only was about € 600. The cost-effectiveness ratios for nicotine replacement therapy (gum and patches) varied from € 3,113 to 8799 per LYG and from € 1,768 to 3,646 per LYG for Bupropion. Only direct medical costs were included. For Bupropion effectiveness data were used from a study that examined the combination with intensive counselling.
Song et al. (2002) evaluated adding pharmacotherapy (nicotine replacement therapy, Bupropion or both) to counselling alone in the UK. Costs per LYG were about $1,441 for nicotine replacement therapy and $ 920 for Bupropion. The impact of smoking cessation on long-term medical expenditure was not considered. The role of discounting in the calculation of the LYG was unclear in this study.
Stapleton et al. (1999) compared GP counselling with nicotine replacement therapy (nicotine patches) with GP counselling only. The incremental cost-effectiveness ratio of nicotine patches and counselling over GP counselling alone varied from £ 398 per LYG (under 35 years) to £ 785 per LYG (55- 65 years). Results were quite robust to changes in both cost and effectiveness estimates. The variables with the greatest impact were the 12-month cessation rate attributable to the intervention and the cost of nicotine patches.

4.5.4 Transferability of foreign study results to the Dutch situation

There are two concerns with respect to the transferability of the results from foreign studies to the Dutch situation. First, the reference scenarios do not exactly reflect the Dutch situation. For example, Song et al. (2002) assumed brief advice or counselling as the basic comparator, whereas this is not the current practice in the Netherlands. Second, although foreign studies concluded that GP counselling in combination with Bupropion would be cost-effective, for the Netherlands no sufficient evidence was found to support the use of that combination (Feenstra et al., 2005a).

The Dutch study has some advantages compared to the other studies. Firstly, besides intervention costs, Feenstra et al. (2005a) also included both the savings for smoking related diseases and the additional costs of health care resulting from an increase in life expectancy. Most studies simply compared intervention costs to health outcomes. Secondly, the Dutch evaluation study covered a broad range of interventions (the individual ones and the ones on population level), evaluating them all in a similar way. Thirdly, Feenstra et al. (2005a) included relapse rates that depend on the time since quit smoking, and smoking prevalence is described as a result of age dependent start rates, and age dependent cessation rates, combined with relapse rates that depend on time since quitting.

4.5.5 Feasibility of implementation in the Netherlands

From a practical viewpoint, implementation of GP counselling aiming at smoking cessation will not be difficult. In the Netherlands, smoking cessation counselling ('H-MIS') is already part of the guidelines for GPs. However, in 2005 only 45% of the GPs applied the H-MIS to at least one of their patients (Jacobs-van der Bruggen et al., 2006). In a report (2006) of the Dutch Institute for Public Health and the Environment, it was estimated that only 2-7% of the smokers is reached by GP counselling in the Netherlands, while 63-65% could be maximal reached (theoretically) should GP counselling be implemented optimally (Vijgen et al., 2006). A shortage of time and a lack of expertise are reasons why GPs do not often give advice about smoking cessation (Frijling and Van der Laan, 2000; Schroeder, 2005).
The effectiveness of GP counselling depends also on the smoker's willingness and compliance. In 2005, 25% of the smokers mentioned they wanted to stop within a year, 15% of the smokers wanted to stop somewhere in the future, 13% never wants to quit and 47% did not know. Taking this into account, a reasonable reach of the individual GP interventions would be a maximum of 30% of the smokers (Vijgen et al., 2006).
Although GP counselling was found to be cost-effective in comparison to the current situation in the Netherlands, the study of Feenstra et al. (2005a) showed that tax increase was the most cost-effective intervention. However, tax measures were not under study here, because this was not considered in the former report of Dirkmaat et al. (2003) and besides that, tax increases were carried out already.

4.5.6 Summary

In the Netherlands, smoking is the risk factor that is associated with the highest burden of disease. Smoking increases the risk of many diseases, such as lung cancer and COPD. The examined studies conclude that smoking cessation interventions, either GP counselling alone, or GP counselling in combination with nicotine replacement therapy would be cost-effective. Less evidence was found for GP counselling in combination with Bupropion. A concern with respect to the transferability of the results from foreign studies to the Dutch situation is that the reference scenarios do not exactly reflect the Dutch situation. Implementation of GP counselling aiming at smoking cessation in the Netherlands is not easy. A shortage of time and a lack of expertise are reasons why GPs do not often give advice about smoking cessation. Besides, the effectiveness depends to a large extent on the compliance of smokers as well.

Cost-effectiveness: **
Transferability: *
Implementation: *

4.6 Influenza vaccination of healthy working adults

4.6.1 Description of the health problem

In the Netherlands, a typical feature of wintertime is an outbreak of influenza. Typical clinical features of influenza include: fever, respiratory symptoms (such as, cough, sore throat, runny or stuffy nose), headache, muscle aches, and extreme fatigue. Some people, older people in particular, develop serious and potentially life-threatening medical complications, like pneumonia. This can be viral pneumonia, in which the influenza virus itself spreads into the lungs, or bacterial pneumonia, in which unrelated bacteria (such as pneumococci, see also section 4.7) attack the person's weakened defenses. Most influenza virus infections are transmitted via virus-laden respiratory droplets.

Influenza viruses are divided into three subtypes: A, B and C. Only the first two types cause important illness and are responsible for the annual epidemics. Only type A has been responsible for pandemics. Influenza epidemics in temperate climates tend to occur on an annual basis. In the Netherlands, the season can start as early as mid-November or as late as the beginning of March. In recent years, the most prevalent episode was January-March. The incidence figures fluctuate considerably each year, because of viral drift: the virus mutates its outer coating from year to year. In 2006, the incidence was 1.6/100,000 (Dijkstra et al., 2006). In the age-group 20-64, the average seasonal incidence of influenza is somewhat lower. Complications of influenza infections are uncommon in this age-group. Therefore, in this age-group admissions to hospital and mortality as a result of influenza are uncommon. However, during each annual influenza epidemic, infections result in significant burden of illness among healthy working adults, especially in terms of absenteeism from work.

4.6.2 Description of the intervention and the current situation in the Netherlands

In the Netherlands, influenza vaccination is particularly recommended for those who are at high risk for developing serious complications as a result of an influenza infection[1]. These high-risk groups include all people aged 65 years and older and people of any age with chronic diseases of the heart, lung or kidneys, diabetes, or immunosuppressed persons. In the Netherlands there is no national influenza vaccination plan focused on healthy working adults. However, in some organizations employees are offered to take part in influenza vaccination programmes, especially in nursing homes and hospitals. The Dutch organization of nursing home doctors and social geriatricians recommends annual vaccination of employees of nursing homes and rest homes (NVVA, 2004).

The main treatment for influenza is to rest adequately, drink plenty of fluids, and avoid exertion. Sometimes, antiviral medication is given, in particular to the following groups of people: non-vaccinated people from high-risk groups, vaccinated people with decreased capacity for antibody production and high risk-groups in case the vaccine appears not to match with circulating influenza strains.

Circulating influenza viruses are subject to permanent changes in strains which require annual adaptation of the influenza vaccine formulation. Updates in influenza vaccine composition should ensure the closest possible match between the influenza vaccine strains and the circulating influenza strains; ensuring this match is one of the foundations for

[1] See De Melker HE, Gerritsen AAM, Hahné SJM (Eds.) for further discussion on this subject.

influenza vaccine efficacy. To what extent this match can be made differs from year to year. Because the influenza viruses differ from year to year, annual vaccination is required.

4.6.3 Results economic evaluations

Studies about influenza vaccination of the whole population (all healthy adults) are left out of consideration. Only studies about immunization programmes that are focused on people that work are examined. In total six studies are included, of which none is performed in the Netherlands (Appendix 7, Table 7.5). Five of them conclude that vaccination will lead to cost-savings. A sixth study calculated the break-even price of the vaccine, estimating the threshold price at which vaccination would be cost-neutral (Nichol et al., 2003). All studies used a societal perspective.

Four of the studies included in this review are simulation studies. One of these (Rothberg and Rose, 2005) was specifically focused on occupational health services and primary care. The other studies did not specify the branch which was under study (Nichol, 2001; Lee et al., 2002; Das Gupta and Guest, 2000). Further reviewed studies were one randomized, double-blind, placebo-controlled study (Nichol et al., 2003) and one observational study (Campbell and Rumley, 1997). Nichol et al. (2003) did their study on employees that were enrolled from 13 recruitment centers. Campbell and Rumley (1997) performed a prospective study in textile plants and outcomes were compared with those of unvaccinated workers in three other plants. Five studies were performed from the societal perspective and one from the perspective of the employer (Das Gupta and Guest, 2002). All studies included indirect costs of production losses as a result of influenza episodes and often, studies include lost work-time for receiving the vaccine. Cost-savings are strongly related to the inclusion of indirect costs and benefits related to production losses and gains. When excluding these indirect benefits, none of the studies remains cost-saving.

Next to direct costs, most studies (Nichol, 2001; Lee et al., 2002; Nichol et al., 2003; Rothberg and Rose, 2005) consider indirect non-medical costs of vaccination, i.e. worker's time needed to get vaccinated. The assumed extent of time investment depends on the organization of administrating the vaccine; at the work place or at the local GP.

Studies differed with respect to the assumed or observed efficacy of the influenza vaccine. The lowest efficacy (24-59%) was used in the observational study of Campbell and Rumley (1997) and the highest efficacy number used was 75% (Nichol, 2001), although this efficacy was only assumed for years with a good match. All of the studies included a sensitivity analysis to evaluate the effects of key parameters on the estimated outcomes. Most studies included efficacy and vaccine price in these estimates. Those studies that concluded that immunization is cost-saving concluded that this result is sensitive to the assumed efficacy of the vaccine. Here, a very important aspect of influenza vaccination has to be emphasized, namely the annually different content of the vaccine. Each year, the viruses that are expected to be most virulent are included in the vaccine. As it is not known on forehand which viruses will be most prevalent in a certain influenza season, the vaccine effectiveness will change from year to year. This will inherently influence the cost-effectiveness of vaccination from one influenza season to the other. Therefore, it is difficult to predict the cost-effectiveness of influenza vaccination with a high probability.

4.6.4 Transferability foreign study results to the Dutch situation

Study results on the cost-effectiveness of influenza vaccination are well transferable to the Dutch situation in general. However, there is one concern. Economic benefits highly depend on the number of workers that choose for vaccination. In most of the considered studies a coverage rate of 100% is assumed. This assumption may be unrealistic. A study about

vaccination in nursing homes in the Netherlands showed that the coverage rate was about 10% in the 2004/2005 season (Van der Sande et al., 2006).
Furthermore, there are some more general issues that endanger the outcomes of the reviewed studies. Whether the expected costs of immunization counterbalance the benefits from decreased absenteeism depends on several factors. Firstly, the type and seriousness of the influenza virus in a certain season determine the benefits from immunization (Nichol and Mendelman, 2004). Secondly, assumptions that are made about the degree of absenteeism and productivity losses due to influenza infections may be unrealistic. A recent Cochrane review showed that vaccination of healthy adults would be effective, but leads to an average decrease of only 0.2 day absenteeism (Demichelli et al., 2005). Moreover, a good match between the vaccine and the circulating influenza strain is a precondition for acceptable outcomes in economic terms. This is sometimes not the case, resulting in a small mean effect (Demichelli et al., 2005).

4.6.5 Feasibility of implementation in the Netherlands

In practice, it will not be difficult to offer the possibility of vaccinating healthy working adults in the Netherlands. Currently, employers can already offer influenza vaccination to their employees (usually at the workplace). The immunization is mainly organized by offices for workplace safety (‘arbodiensten’) and there are several commercial influenza vaccination services. However, there are some factors that will hamper the implementation of vaccination. Since influenza has a relatively harmless course for people that do not belong to the high-risk groups, and vaccination is only partly effective, vaccination is not indispensable. As vaccination coverage is always strongly associated with perceptions of the severity of disease, one can expect that this will also be the case for influenza vaccination. Although studies showed that indirect benefits of averted production losses were important to the cost-effectiveness of the intervention, also non-economic reasons may be important. It is argued that vaccinating working adults could have extra benefits of increasing vaccine coverage among high-risk working adults and potential external benefits (increasing herd immunity) if workers are in occupations requiring a high level of contact with high-risk groups (for example health-care workers). However, vaccinating health-care workers did not appear efficacious against influenza among the elderly people they care for in institutions (Thomas et al., 2006).

4.6.6 Summary

Although complications of influenza infections are uncommon among healthy working adults, infections result in a significant burden of illness, especially in terms of absenteeism from work. Most studies conclude that vaccination will lead to cost-savings when the societal perspective is chosen. Economic benefits highly depend on the number of workers that choose for vaccination, the actual match for the season, the virulence of the circulating strains, and the degree of absenteeism and productivity losses due to influenza infections. In practice, it will not be difficult to offer vaccination to healthy working adults in the Netherlands. However, vaccination coverage is always strongly associated with perceptions of the severity of disease, and since influenza is in general not perceived to be a serious health threat, one can expect that this will also be the case for influenza vaccination.

Cost-effectiveness: *
Transferability: *
Implementation: **

4.7 Pneumococcal vaccination of elderly persons

4.7.1 Description of health problem

Pneumococcal disease is caused by an infection with the bacterium *Streptococcus pneumoniae* (the pneumococcus). There are at least ninety different kinds (serotypes) of the pneumococcus. Only a limited number of serotypes cause the majority of severe pneumococcal diseases. Infections with the pneumococcus can be either invasive or noninvasive. The invasive infections occur as septicemia, meningitis and pneumonia associated with bacteria in the blood (bacteremia). *Streptococcus pneumoniae* causes also noninvasive pneumococcal infections, such as bacterial pneumonia, mucosal infections, like inflammation of the middle ear (otitis media) and sinusitis. The disease develops in only a small proportion of the infected persons, especially in young children, the elderly, and people with low immunity. A total of 5-20% of the pneumococcal pneumonia is complicated with a bacteremia. The incidence of pneumococcal bacteremia in people 65-79 years is about 19.5/100,000. Among people older than 80 years the incidence is 37.4/100,000. The mortality from invasive infections among people aged 65 and older is 30-50% (Van Furth, 2000).

4.7.2 Description of the intervention and the current situation in the Netherlands

Pneumococcal diseases can be treated with antibiotics. For prevention, two types of pneumococcal vaccines are now licensed in Europe, and include a variable number of capsular serotypes (bacteria that are sensitive to the vaccine): the 23-valent pneumococcal polysaccharide vaccine (PPV) and the conjugated 7-valent pneumococcal vaccine (PCV)[1]. PPV provides protection against invasive pneumococcal disease caused by 23 serotypes in subjects older than two years. PCV protects against seven serotypes, but provides also long lasting immunity against invasive disease in those younger than two years.

In the Netherlands, in contrast to many EU-countries, vaccination against pneumococcal disease for elderly people is not routine. Among adults and elderly, the vaccine is administered only to individuals who are at substantially increased risk of pneumococcal infection, like people with immune system impairment and splenectomy patients (Dutch Health Council, 2003). Since April 2006, vaccination with the conjugated 7-valent pneumococcal vaccine is included into the National Immunization Programme. This vaccine has proven to be very effective against invasive pneumococcal disease in children (Black et al., 2000). Moreover, the vaccine has reduced carriage of pneumococci resulting in reduced transmission to the elderly, i.e. herd immunity (Lexau et al., 2005).

4.7.3 Results from economic evaluations

Nine economic evaluation studies on elderly vaccination with the 23-valent pneumococcal polysaccharide vaccine are examined in this report (Appendix 7, Table 7.6). Two of these are carried out in the Netherlands (Baltussen et al., 1997; Postma et al., 2001). The cost-effectiveness ratios in the different studies vary from cost-saving to 24,872 ECU per QALY. The assumed effectiveness of the polysaccharide vaccine against invasive disease in the elderly is important for the benefits of immunization. Studies vary in their assumptions on the efficacy of the vaccine, ranging from 55% for 5 years (all people ≥ 65 years) to 70-90% for five years (people aged 65-69 years). One study estimated the threshold of the vaccine's effectiveness at which vaccination would be cost-neutral, besides the costs per life year

[1] See De Melker HE, Gerritsen AAM, Hahné SJM (Eds.) for further discussion on this subject.

gained (Mangtani et al., 2005). None of the studies have used empirical data about the effectiveness of the vaccine in their modelling approach. Most economic evaluations have chosen to rely on efficacy data from observational studies rather than trials. However, in sensitivity analyses it turned out that vaccine effectiveness was the most influential variable.

Some studies gave specific outcomes for age-groups and high-risk groups. Baltussen et al. (1997) concluded that cost-effectiveness rates improve with higher age of the target group for vaccination. Most (more recent) studies (Sisk et al., 1997; De Graeve et al., 2000b; Postma et al., 2001; Mukamel et al., 2001; Amazian et al., 2002; Melegaro and Edmunds, 2004) applied lower vaccine efficacies for older age groups. This had consequences for the relationship between age and cost-effectiveness of vaccination. For instance, Sisk et al. (1997) found that cost-effectiveness ratios improved with increasing age until the age of 75 and above that age the ratio declined with increasing age.

Studies differ with respect to the kind and level of costs that are incorporated. For example, the study of Silk et al. (1997) included also costs that occur in years of life that would not were lived without the intervention. Also, the vaccination costs vary between studies. Four economic evaluations calculated the cost-effectiveness of pneumococcal vaccination, assuming that the vaccine was offered alongside the influenza vaccine (Mukamel et al., 2001; Amazian et al., 2002; Melegaro and Edmunds, 2004; Mangtani et al., 2005). This assumption in fact reflects the Dutch situation best, because influenza vaccination is particularly recommended for people aged 65 and older. Amazian et al. (2002) showed that the cost-effectiveness of pneumococcal vaccination is worse when the vaccine is not given at the same time as vaccination against influenza. Studies from Mukamel et al. (2001), Melegaro and Edmunds (2004), and Mangtani et al. (2005) do not make this comparison, and therefore, diverge from to the other considered studies.

Difference in results can be partially attributed to the inclusion or non-inclusion of noninvasive infections. Some studies assume that the vaccine also has a protective effect on infections with a noninvasive course (Baltussen et al., 1997; De Graeve et al., 2000a). Other studies analyzed the effects on invasive disease separately (De Graeve et al., 2000b (only meningitis); Mangtani et al., 2005) or solely (Sisk et al., 1997; Postma et al., 2001; Amazian et al., 2002; Mukamel et al., 2001; Melegaro and Edmunds, 2004). However, a protective effect on noninvasive infections is controversial. Including a protective effect on noninvasive infections overestimates the benefits of the vaccination. The studies in which this was done, resulted in cost-savings. These outcomes are hypothetical until it can be proved that (new) vaccines are effective against noninvasive diseases (Beutels and Postma, 2001).

4.7.4 Transferability foreign study results to the Dutch situation

An important determinant of cost-effectiveness of the pneumococcal vaccination is the assumed incidence of invasive diseases caused by pneumococci. Most studies assume a higher incidence than the incidence that is found in the Netherlands (19.5/100,000 for people 65-79 years). For that reason vaccination may work out less favourable in terms of cost-effectiveness in the Netherlands.

Four studies reflect the Dutch situation by assuming that pneumococcal vaccination takes place alongside influenza vaccination. However, only the costs reductions are taken in consideration, leading to more favourable cost-effectiveness outcomes. The conceivable interdependence between both, influenza vaccination and pneumococcal vaccination, is not

taken into account. Since it is not certain to what extent influenza vaccination reduces the number of invasive pneumococcal infections the effectiveness of pneumococcal vaccination is unknown. That is the reason why the Dutch Cochrane Centre and the National Health Council concluded that there is insufficient evidence for implementation of pneumococcal vaccination besides the influenza vaccination for people aged 65 and over (Dutch Health Council, 2003).

It is known that vaccination in children diminishes the incidence of pneumococcal disease among the elderly (herd immunity). Since 2006, infants in the Netherlands are vaccinated with the conjugated 7-valent pneumococcal vaccine. One can expect that the burden of disease among the elderly caused by the seven serotypes will decrease following the introduction of infant vaccination. Therefore, the use of the polysaccharide vaccine among the elderly may become less cost-effective in the future.

4.7.5 Feasibility of implementation in the Netherlands

The pneumococcal vaccine could be administered to the elderly at the same time as the influenza vaccine or during routine medical consultation. It should be considered before implementation whether vaccination against pneumococcal disease has an impact on the influenza vaccination coverage (Van den Bosch, 2002). It is not known in how far the uptake of influenza vaccination will be influenced by an additional vaccination at the same time.

4.7.6 Summary

A bacterial infection with *Streptococcus pneumoniae* causes noninvasive infections and invasive diseases such as meningitis, septicaemia and pneumonia, generally associated with bacteremia. The incidence of pneumococcus bacteremia is about 19.5/100,000 in people 65-79 years and 37.4/100,000 in people older than 80 years. The cost-effectiveness ratios range from cost-saving to 24,900 ECU per QALY. Converting this to 2005 Euros will result in a range from cost-saving to € 31,000 per QALY. There are several threats to the transferability of foreign study results to the Dutch situation: a lower incidence of invasive diseases caused by pneumococci and the feasible interdependency between influenza vaccination and pneumococcal vaccination. Most likely, pneumococcal vaccination will be easily implementable in the Netherlands, because it can be given at the same time as influenza vaccination. However, it may be that vaccination against pneumococcal disease influences the influenza vaccination coverage degree.

Cost-effectiveness: *
Transferability: *
Implementation: **

5. Conclusion and discussion on part A of this report

5.1 Main findings from part A of this report

This report is the third in a series of reports that aim to identify cost-effective preventive interventions that have not yet been diffused into the Dutch health care system or into a public health setting. In this report, five new interventions are presented and at the same time, updated information on cost-effectiveness and implementation issues for six interventions that were described in less detail in one of our previous reports. For all 11 interventions, brief information on the magnitude and character of the health problem is presented, along with information on the intervention, its cost-effectiveness, and issues related to the transferability of foreign study results to the Dutch situation. Besides, attention is paid to possible future implementation of the intervention in the Netherlands by describing the pros and cons of implementation. For each intervention, the findings with regard to cost-effectiveness, transferability issues and implementation issues are summarized using a two-star system, as described in chapter 2, sections 2.2.5 to 2.2.8. Table 5.1 shows our main findings, using this two-star system with regard to the three key elements that determine whether a preventive intervention shows great promise or not.

Table 5.1: Summary of main findings with regard to cost-effectiveness, transferability and implementation issues

	Cost-effectiveness [a]	Transferability [b]	Implementation [c]
New identified interventions (chapter 3 of the current report)			
Screening for neonatal group beta streptococcal infections	**	*	**
Universal hepatitis B vaccination	*	*	*
Rotavirus vaccination of newborns	*	*	*
Pertussis vaccination of adolescents	*	*	*
Human papillomavirus vaccination of adolescents	*	*	*
Update of interventions from previous report (2003) (chapter 4 of the current report)			
Fluoridation of drinking water	**	*	*
Mandatory folic acid fortification of staple foods	**	*	*
Vaccination against varicella zoster virus	**	*	*
Stop smoking interventions	**	*	*
Influenza vaccination of healthy working adults	*	*	**
Pneumococcal vaccination of elderly persons	*	*	**

a) For **cost-effectiveness** the stars represent:
* Moderate evidence: three or more studies show cost-effectiveness, defined as:

- The range of possible values (either from sensitivity analyses or uncertainty analyses) often exceeds the threshold value of € 20,000 per QALY/LYG and/or some studies show a point-estimate in the Base Case analysis that exceeds € 20,000 per QALY/LYG and/or a cost-effectiveness acceptability curve shows a considerable probability That the cost-effectiveness threshold exceeds € 20,000 per QALY.
- Benefit to cost ratios < 1 are reported.
- Costs per case averted above the expected cost per case are reported.

** Strong evidence: three or more studies show cost-effectiveness, defined as:

- The range of possible values of the cost-effectiveness ratio (either from sensitivity analyses or uncertainty analyses) does not exceed € 20,000 per QALY/ LYG and/or a cost-effectiveness acceptability curve shows that the probability that the cost-effectiveness ratio remains below € 20,000 is high.

b) For **transferability** the stars represent:
* Major problems with transferability of foreign study results to the Dutch situation, more research in the Dutch context is necessary.
** Results of foreign studies can easily be transferred to the Dutch situation.

c) With respect to **implementation issues** the stars represent:
* some or major problems were expected with regard to organizational / infrastructural issues and/or ethical concerns.
** it is anticipated that implementation of the intervention in the Netherlands is feasible, implying no major problems with regard to organizational / infrastructural issues and/or ethical concerns.

Table 5.1, summarizes our main findings on cost-effectiveness, transferability of foreign study results to our country and implementation issues for 11 preventive interventions. An 'ideal' intervention should have two stars for all three relevant aspects. No single intervention was given two stars for all three relevant aspects. Three interventions were found to be very cost-effective and at the same time, no major barriers for implementation were found. These are screening for neonatal group beta streptococcus infections, influenza vaccination of healthy working adults and stop smoking interventions in a GP practice. Three more interventions were found to be very cost-effective, but here, barriers towards implementation were found. These interventions are folic acid fortification of staple foods, water fluoridation to prevent dental decay and vaccination against varicella zoster. For two interventions, implementation was described to be feasible, while some questions surrounding the cost-effectiveness of the intervention in the Dutch situation still remain. These are pneumococcal vaccination of elderly persons and pertussis vaccination of adolescents. With regard to transferability of foreign study results to the Dutch situation, it is concluded that almost all interventions need adaptation of foreign results to the specific Dutch context.

5.2 Discussion of results

This report is the third report in which is focused on preventive interventions that may be promising. The first report, however, was an explorative study and the criteria used for cost-effectiveness were different from ones used in the second and third report. The first report did not use the criterion that at least three good economic evaluations had to be available and it also included interventions that were already implemented in the Netherlands. Furthermore, the cut-off point of € 2500 per QALY was used. The aim of that first report was merely to demonstrate that many (existing) preventive interventions are very cost-effective or even cost-saving. The aim of the latter two reports was more to identify promising preventive interventions, which might be interesting to introduce in the Netherlands. Because methods used for the three reports were not uniform, all interventions of the first report were re-investigated, using the same criteria that were used in the second report. The results of this re-investigation are described in the current, third report. In this chapter our findings are discussed, as well as the limitations of our study.

Updating interventions from the 2003 report

As can be seen in Table 5.1, several promising interventions were identified or updated in this report. The 11 interventions in this table were all assessed using similar methodology. This implies that the interventions identified in the 2003 report were re-assessed using more strict inclusion criteria in comparison with the ones used for the 2003 report. From the 18 interventions that were identified in the 2003 report, 8 were implemented in the Netherlands or will be implemented in the near future. This left 10 interventions for the update using the current, more restricted, criteria. Unfortunately, the update resulted in an exclusion of 4 interventions that were identified before. Several reasons contributed to the current decision to exclude interventions. These could either be related to the fact that three good quality studies showing cost-effectiveness could not be identified, as was the case for the reduction of fat consumption to reduce heart disease and vascular diseases and interventions to promote breastfeeding, or to the fact that the intervention itself showed a large diversity in the way it was operationalized, as was the case with interventions to prevent falls of elderly people and with hepatitis A vaccination of certain groups of employees. Details on the reason why interventions from the 2003 report were excluded in the current report can be found in Appendix 2.

The use of a two-star system for cost-effectiveness, transferability and implementation issues

In the previous report (Vijgen et al., 2005), a two-star system to indicate the level of cost-effectiveness of preventive interventions was used for the first time. In comparison with the 2005 report, more attention was paid to transferability of foreign study results and to implementation issues. In the current report, the two-star system was extended to these other relevant issues. As appears from our results (summarized in Table 5.1), the two-star system is hardly distinguishing the preventive interventions with regard to the issue of transferability. The conclusion can easily be drawn that foreign study results can hardly ever be directly translated to the Dutch context. This implies that decision makers can not rely solely on results of foreign cost-effectiveness studies, when considering the implementation of a preventive intervention in the Netherlands. It will always be necessary to pay attention to cost-effectiveness in the Dutch context, either with a full Dutch cost-effectiveness study or with a careful assessment whether the foreign results will be more or less positive in the Netherlands. Only in a situation where it is estimated that all relevant factors (as appears from sensitivity analyses) are more positive for the Netherlands, and thus are affecting cost-effectiveness in a sense that the ratio decreases, a decision maker can rely on foreign results. Such a situation will be very rare.

In contrast to the former report, implementation issues have now also been evaluated with a two-star system, giving a relatively equal weight to cost-effectiveness and feasibility of implementation. This reflects the actual situation in decision making, since it is impossible to implement even the most cost-effective or cost-saving intervention when major resistance within society is present or when financial, organizational or infrastructural issues make implementation impossible. However, in contrast to the evaluation of cost-effectiveness, the evaluation of the feasibility of implementation is done in a more qualitative way, as it is based on interviews with Dutch experts in the field of these preventive interventions. By using a two star system for both cost-effectiveness and implementation, a relatively heavy weight is given to the qualitative assessment of feasibility of implementation, and thus to the vision of the experts that were interviewed. The assessment of feasibility of implementation could be given more weight using instruments such as a consensus meeting where every possible stakeholder is invited to reflect upon the issue. Such consensus meetings were used

before, i.e. a consensus meeting on the necessity to start a national screening programme for colon cancer that was organized by ZonMw, and could be used again in the future, should decisions to start with the implementation of major preventive programmes have to be taken. However, in the context of this report series, such methods are hardly applicable. A first step to a more objective method for the appraisal of feasibility of implementation is to develop a checklist with all the relevant topics that might play a part. This should be done in close cooperation with ZonMw, the Netherlands Organisation for Health Research and Development. Future reports within this project should make use of such an implementation checklist.

Information on cost-effectiveness is only one aspect of decision making

The information presented in the report contributes to the assessment of the preventive intervention. It is meant to support future decision making on the implementation of the interventions. However, such decision making is not only based on the cost-effectiveness but also on other aspects. These aspects include, among others, total budget impact of the intervention (what is the magnitude of the group at which the intervention is targeted, hence what will be the total budget impact of introduction of the new preventive intervention?), equity considerations (does the intervention contribute to the decrease of socioeconomic disparities in health?) and disease impact, both at the national level (what is the total DALY loss associated with the disease?) and at individual level (what is the impact of the health problem on the individual and his/her family?) (De Wit and Schuit, 2006). Hence, cost-effectiveness is only one element in the decision making process, but not an unimportant one. Especially with respect to the implementation of large screening programmes and the introduction of new vaccines in the National Immunization Programme, cost-effectiveness traditionally plays a large role.

Only information on cost-effectiveness, not on cost-ineffectiveness

A consequence of the chosen methods is that only interventions were listed that have at least three good quality economic evaluations showing cost-effectiveness (defined as cost per QALY of maximal € 20,000). Although this is informative with regard to future decision making on the nationwide implementation of one or more of these interventions, this focus on cost-effective interventions results in more or less ignoring the knowledge of which interventions are less cost-effective or even cost-ineffective. Such knowledge could also be informative for health policy makers, either because it makes clear that some interventions should not be introduced or that existing interventions should become redundant. However, it should be noted that publication bias might hamper the attempt to identify cost-ineffective interventions, as it is usually more difficult to publish negative study results.

An example of a study that presents information on both cost-effective and cost-ineffective interventions is recently published by Maciosek et al. (2006). They concentrated on clinical preventive services and prioritized all available information by awarding maximal five points to the level of cost-effectiveness (using 1 point for interventions with a cost-effectiveness ratio ≥ US $ 165,000 / QALY and 5 points for interventions that are cost-saving) and also by awarding maximal 5 points to the clinically preventable burden, ranging from < 15,000 QALYs (1 point awarded) to ≥ 360,000 QALYs (5 points awarded). Here, priorities for further introduction of preventive interventions were established by comparing the total ranking (maximum total score of 10 points) with what is known about the current rates of use of these clinical preventive services (estimated as a percentage of what is being considered as the optimal use of the preventive intervention). One difference in the focus of Maciosek et al. (2006) and the current focus is of course that they focus on existing clinical preventive

services, and that we try to identify new and interesting interventions from the whole field of prevention, including health promotion, health protection and health in all policy. However, in future research, we could extend the assessment method that currently consists of information with regard to cost-effectiveness, transferability and implementation, to a system that also includes quantitative information on the preventable disease burden. Then, it should also be explored whether other important characteristics of prevention, such as total budget impact and equity aspects could be introduced in our assessment method. One additional advantage of such an extended assessment method is that it will be easier to link information from the work to the priorities for prevention, as communicated by the Ministry of Health, Welfare and Sportsin the recently launched *Tweede Preventienota* 'Kiezen voor gezond leven' (Ministerie van VWS, 2006). In this Government White Paper, five priorities for prevention were launched, namely smoking, problematic alcohol use, depression, overweight (physical activity and nutrition) and diabetes mellitus. At present, none of the five new interventions as described in this report are related to these priorities. Coincidentally, all newly identified interventions are related to infectious diseases. From the interventions that were described in earlier reports (see Table 1.1.), only seven interventions are targeted at one of the five national prevention priorities. Therefore, concluded is that there is an urgent need for more effectiveness and cost-effectiveness studies of interventions that address the health problem areas as defined in the Tweede Preventienota.

Prioritising cost-effective interventions

It may be worthwhile to build upon the information described in the three RIVM reports (Dirkmaat et al., 2003; Vijgen et al., 2005; current report) by prioritizing the interventions with respect to importance of implementation in the Dutch healthcare or public health system. This could be done using a system such as presented in Maciosek et al. (2006) (described above) or with panel sessions, for instance panels of health care workers, citizens and/or healthcare policymakers. Such a prioritization exercise could become part of the next Volksgezondheids Toekomst Verkenning (Public Health Status and Forecast report) in 2010. However, in order to do so, a prioritization system should be developed in the next two years. This prioritization system could build on recent work performed in this field, for instance by the Raad voor de Volksgezondheid en Zorg (2006) and on previous work by other authors, such as Stolk (2004). Foreign experiences with prioritization, for instance those of the US Committee on Clinical Preventive Service Priorities (Coffield et al., 2001; Maciosek et al., 2006), could also be taken into account. A prerequisite for prioritization different interventions is that comparable outcome measures (costs per (quality adjusted) life year gained) are used. As can be seen from Tables 6.1 to 7.6, the included studies report various outcome measures. For instance, when 'cases prevented' refer to young persons this represents much more QALYs gained as compared to older persons. This makes cost-effectiveness ratios based on these different outcome measures incomparable among each other. So for a prioritization exercise only those studies that report costs per QALY can be included.

Early warning system

Starting with the 2005 report, strict conditions are used for evidence. Only those interventions with at least three good-quality studies that describe cost-effectiveness were included. Only those interventions for which *all available* studies report cost-effectiveness ratios under € 20,000 per QALY are rewarded with the maximum score of two stars for cost-effectiveness. As a result of the use of this strict selection criterion, it is increasingly difficult to describe really new cost-effective preventive interventions, simply because new interventions have not been rigorously tested for their cost-effectiveness. Of course, that does

not imply that these interventions are not promising or that they *are* not cost-effective. It might be interesting to extend the current research and add a separate section on *early warning* in the future reports. This could be based on effectiveness studies with limited information on cost-effectivity and/or on own modelling work to explore the cost-effectiveness of interventions in a more crude way. Such an *early warning system* may be input for research programming by e.g. ZonMw, the Netherlands Organisation for Health Research and Development. ZonMw could use information from such an early warning system to specifically call for research proposals investigating the cost-effectiveness of selected intervention(s) in the Dutch context. Furthermore, the link to the modelling part of the project (part B of this report) could also be improved by exploring the costs and effects of future implementation of interventions with limited evidence on cost-effectiveness, using a modelling exercise. Such early modelling can identify the key data that need to be available for a more final cost-effectiveness analysis, and will inform research programmers and policy makers which information is still needed before a well-informed decision on implementation of the intervention can be made.

Use of strict criteria to assess whether new interventions are promising has disadvantages too

As discussed above, the methods and criteria to select interventions and characterize them as promising for public health policy have some disadvantages too. One major disadvantage is that we were asked by the Ministry of Health, Welfare and Sports to only select those interventions with health effects within the next five years. Many interventions, for instance interventions to promote the intake of healthy food, have effects in the longer term only. However, interventions that are effective in the long term may still be cost-effective, and as such promising for public health policy. The inclusion of a longer time horizon in future research is strongly supported.

Also, the strict criteria for inclusion of interventions, mainly the criterion that three good quality studies have to be available, prevent the identification of preventive interventions that differ slightly in the way they are executed in previous cost-effectiveness research. For instance, several good quality economic evaluations were found evaluating the prevention of accidental falls in elderly persons, but the interventions itself were not always comparable. For instance, some publications described a home hazard reduction programme while other publication evaluated such a home hazard reduction programme with medication adjustments and targeted exercise programmes. Another example is the vaccination against hepatitis A virus for selected groups of employees. Publications describing the cost-effectiveness of vaccination of military staff, traveling frequently to endemic regions, for vaccination of people working in nurseries and other employees working with young children, and for food industry workers were found. It is possible that these types of interventions might be interesting within the Dutch public health context, but the sole argument that less than three good quality economic evaluations are available hampers the inclusion of this intervention in the report. An early warning system, as described above, could provided with room to describe interventions that are possibly interesting within the Dutch context, but for which three or more high quality economic evaluations are not yet available.

One further disadvantage the methodology used is that for some preventive interventions one can only discuss one preventive strategy, namely the one that was evaluated in at least three studies of good quality, while more strategies are available. Sometimes, it would be more interesting to discuss all prevention options for one health problem in a more integral way. One example is the prevention of hepatitis B. In this report, studies were discussed evaluating

the universal vaccination of infants. In a low endemic country such as the Netherlands, this is just one option for prevention policy. Other options include the vaccination of risk groups, adolescents, certain groups of immigrants, and certain groups of employees. Such a more integral approach towards all prevention policies that are available is only possible in a situation where the criterion that at least three good quality studies have to be available is relieved a bit. Possibly, this could also fall within the outline of an early warning system, as proposed above.

Cost-effectiveness primarily known in the area of disease prevention

As in previous reports, the conclusion is made that *disease prevention* is the area that was evaluated best with regard to its cost-effectiveness. Out of the eleven interventions described in detail in this report, eight interventions are from the disease prevention area, two from the health protection area (fluoridation of drinking water and folic acid fortification of flour) and one stems from the health promotion area (stop smoking interventions). No single interventions were identified from the health in all policy area, as in previous years. In their review of the cost-effectiveness of preventive policies, Goldsmith et al. (2004) found that health in all policy interventions do not always incorporate health outcomes in their evaluations. By definition, these interventions have multiple health and social outcomes that sometimes are difficult to quantify. However, a major requirement for adding a sound economic evaluation to these interventions is not fulfilled if health effects are not measured. Several authors have also described the difficulties in properly determining the (cost-))effectiveness of community prevention programmes (Carande-Kulis et al., 2000; Thomson et al., 2004; De Wit and Brouwer, 2004). Insufficient funding for evaluating health promotion interventions, especially in comparison with pharmaceuticals and medical technology, further disadvantages the growth of the economic knowledge on prevention. However, unlike the situation with large screening or vaccination programmes, economic evaluation has so far not played a well-defined role in decision making around health promotion activities, health protection measures or health in all policies. In a situation where economic evaluation becomes a mandatory element in the decision making process, public health funding would severely be discriminated in comparison with the disease prevention field, simply because not everything that counts can be counted and not everything that can be counted counts.

Vaccinations

Four out of five interventions that are described for the first time in the current report are new vaccines for infectious diseases. Indeed, many new vaccines are being developed, tested and marketed at present (De Melker et al., 2005). A decision to implement new vaccines in the National Immunization Programme is a complicated one. Besides the considerations that are key in any implementation decision on preventive interventions, such as budgetary consequences and disease impact, some very specific questions have to be answered satisfactorily before new vaccines can be introduced in the Netherlands. Among these issues are vaccine safety, both of stand-alone vaccines and of combination vaccines, the total number of vaccinations that is acceptable for children and their parents, the consequences of more vaccinations on vaccine compliance and therefore, on the level of herd immunity. The Centre for Infectious Diseases Control of the RIVM publishes an annual report on the status quo of candidate vaccines for the National Immunization Programme. In this report, factual information on all relevant other aspects of vaccine introduction, besides cost-effectiveness, is given. It is clear that not all vaccine candidates can be introduced at the same time. This would not only require large investments, but probably also be not acceptable for both parents and health care workers involved in the National Immunization Programme. However, two of the vaccines described in this report are vaccines that (also) protect against

sexually transmitted diseases. These vaccines may also be given at a later age than early childhood, for instance during adolescence. This opens the discussion whether adolescent vaccination should be introduced in the Netherlands. A Health Council committee advises the ministry on the future content of our National Immunization Programme. The next advice is due in December 2006. It is anticipated that the Health Council committee will include considerations on all four vaccines described in the current report in his advice, and also that the committee reflects upon the introduction of adolescent vaccination in the Netherlands.

Use of different perspectives
It is difficult to compare the results of different economic evaluations, even for one preventive intervention. One major reason for these difficulties is that studies use different perspectives. Study outcomes in terms of cost-effectiveness ratio may differ largely when different perspectives are used (Feenstra et al., 2006; Drummond et al., 2005). Often, interventions are cost-saving or very cost-effective from a societal perspective but less efficient from a payer perspective. Therefore, one should always note from which perspective a study was done. One apparent example is varicella vaccination. Here, the programme costs are most likely born by society (via the Ministry of Health's budget for the National Immunization Programme), while the principal beneficiary of the positive economic effects are employers, because it is less likely that parents have to stay at home with their sick children. From the payer's perspective, the investment in varicella vaccination may still be interesting, but primarily for other reasons than economic reasons, since the investment will not pay back via reduced treatment costs. However, in circumstances were prevention still requires a net payment from the payers' perspective, the issue of opportunity cost becomes a prominent one. This implies that the investment in one activity is associated with the need to forego another activity. As the total prevention budget is limited by definition, investments in efficient preventive programmes sometimes cannot be made.

5.3 Directions for further research

Following from the remarks that were made in the previous section, conclusions are made for this part of the report by summarizing some directions for future research. We will distinguish between directions for the own future research and directions for future research in general.

Directions for future RIVM research:
- The 21 preventive interventions that were identified in the three successive RIVM reports should all be assessed using similar methodology (i.e. methodology as used in the current report). As the current report contains an update of the interventions described first in the 2003 report, the practical implication of this remark is that the ten different preventive interventions that were introduced in the 2005 report (Vijgen et al., 2005) should explicitly be assessed with regard to transferability of foreign study results to the Dutch context and with regard to implementation aspects.
- The assessment method currently used in our reports (focusing on cost-effectiveness, transferability of foreign study results, and implementation aspects) should be extended with quantified information on the preventable disease burden. Furthermore, it should be explored whether other important aspects of prevention, such as total budget impact and individual burden of disease (e.g. disability weights), can be introduced in the assessment method.

- All available information for 21 (or possibly more in the years to come) preventive interventions should be prioritized. This could be done in the context of the next Public Health Status and Forecast report that is scheduled for 2010. In the next two years, a prioritization system should be developed further.
- The work for this report series could be extended with an *early warning* section, in which promising effective interventions are identified. If economic information is not yet available but interventions otherwise appear to be implementable in the Netherlands, ZonMw could specifically invite the research community to submit targeted research proposals. This will enhance the link between the work as being done in the context of these report series and research programming by ZonMw. Also, preliminary modelling of cost-effectiveness of implementation in the Netherlands could point out which parameters need to be further explored in a Dutch context.
- The time horizon for effectiveness of interventions to be selected, which is currently set at the next five years, should be extended to a longer time horizon, for instance 20 to 50 years in the future.
- New interventions that appeared not to be cost-effective should also be listed in future reports.

General directions for research on cost-effectiveness of prevention:

- There is a need for systematic reviews of effectiveness of health promotion activities, health protection measures and healthy public policy interventions. For those interventions that appear to be effective but for which economic evidence is lacking, economic evaluations should be performed. Here, again a link can be made between this work and research programming by ZonMw.
- Preventive activities that were implemented long ago should be re-evaluated for their cost-effectiveness, regarding changes in the health care and public health context since its introduction.
- There is an urgent need for more effectiveness and cost-effectiveness studies of interventions that address the five major health problems in the Netherlands, as defined in a recent Government White Paper on Prevention (Tweede Preventienota).
- The study found that foreign studies are never easily transferable to the Dutch situation. For the major factors that determine the cost-effectiveness of a specific intervention (as determined by sensitivity analyses / uncertainty analyses), it will always be necessary to look at the Dutch situation. Hence, decision makers should never rely on foreign cost-effectiveness analyses alone when a decision on implementation of new preventive interventions has to be made.

Part B: Modelling effects of nationwide implementation of new preventive interventions

6. Introduction

6.1 Outline part B

In the previous report on economic evaluations of preventive interventions, several cost-effective interventions that were not systematically implemented in the Netherlands were identified (Vijgen et al., 2005). Many of these interventions only had evidence from international cost-effectiveness analyses. To estimate the cost-effectiveness of implementation of these preventive interventions in the Netherlands, two of these interventions were selected for further analysis: the prevention of recurrent depression by maintenance cognitive behavioural therapy, and the prevention of chronic diseases by pharmacologic treatment of obesity. These interventions were assumed not to have major barriers for implementation, and their cost-effectiveness has not yet been modelled in the Netherlands. Chapter 7 presents the modelling study on the costs and effects of the prevention of recurrent depression by maintenance cognitive behavioural therapy. Then, chapter 8 contains the modelling study on the costs and effects of the prevention of chronic diseases by pharmacologic treatment of obesity. This is followed by a general discussion (chapter 9). Before proceeding, the general methodology is described and it is elaborated on how the results should be interpreted.

6.2 Methodology and the role of uncertainty

A crucial element of all economic evaluations is the perspective that is taken in the analyses. The perspective of an economic evaluation determines what costs and effects are taken into account (Brouwer and Koopmanschap, 2000). For instance, if the perspective of a study is that of the patient, only costs that are relevant for the patient, like travel costs, are taken into account while costs of medical treatment are ignored (assuming the patient does not have to pay for these costs). The two cost-effectiveness studies presented in this part were both evaluated from a health care perspective. This means that all differences in medical costs over the modelled time horizon were taken into account, and that is was assumed that the interventions, if implemented, would be paid for by parties belonging to the health care system. Taking into account differences in lifetime health care costs means that if the intervention extends life, also so-called medical costs in life years gained are taken into account (Van Baal et al., 2006b). In accordance with the guidelines for pharmacoeconomic research, effects and costs were discounted at 1.5% and 4.0% annually (Rodenburg – Van Dieten, 2005).

To estimate effects of new preventive interventions, models are needed that combine information from many different data sources (Griffin et al., 2006; Sculpher et al., 2006). Since in most cases a lot of parameters (i.e. the effects of treatments) are not well-known, uncertainty of those parameters influences the outcome of the study. To reflect uncertainty in model parameters on outcomes, we have employed probabilistic sensitivity analysis (PSA). In this analysis, uncertainties are defined for the input data in the model. One then randomly draws new input data from the uncertainty distribution, and feeds this into the method, yielding a new result. This process is repeated e.g. 1000 times, and the variability

of the 1000 results from this process reflects the uncertainty about the outcome of the method. In a cost-effectiveness analysis, outcomes are incremental costs and effects of an intervention. Figure 6.1 displays the outcomes of a PSA in a so-called cost-effectiveness plane of a hypothetical intervention (Intervention A).

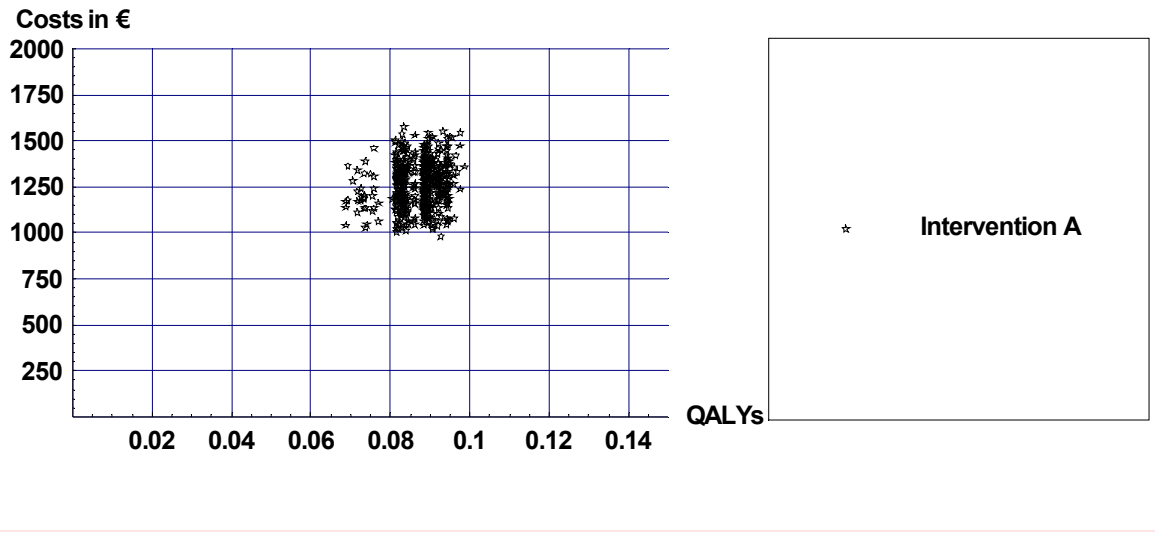

Figure 6.1: Example of a cost-effectiveness plane

By dividing the mean incremental costs (the numerator) by the mean incremental QALYs (the denominator) an incremental cost-effectiveness ratio (ICER) is obtained. In the example of Figure 6.1 the ICER equals € 15,000 per QALY gained.

Another way to present uncertainty around the ICER is through the use of a cost-effectiveness acceptability curve (CEAC) (Fenwick et al., 2001). In a CEAC, the probability that an intervention is most cost-effective compared to its comparators is displayed as a function of the monetary value attached to a QALY (also called the threshold). By attaching monetary values to a QALY one can calculate the net monetary benefit on an intervention. If for instance a QALY is valued € 10,000 the net monetary benefit can be calculated by multiplying the QALYs gained with €10,000 and then substract the incremental health care costs. The CEAC can be plotted by calculating the net monetary benefit for different values of the threshold for all values of the outcomes of the PSA for all possible interventions. Figure 6.2 displays a CEAC for the hypothetical intervention A compared to usual care. What can be derived from Figure 6.2 is that the probability of intervention A to be cost-effective increases as the threshold increases. Vice versa, the probability that usual care is cost-effective decreases as the threshold increases. Given a threshold of € 20,000 intervention A has the highest probability of being cost-effective. However, should the threshold value be € 10.000 per QALY, it is more likely that usual care is most cost-effective. It should be noted that the intervention with the lowest ICER does not necessarily have the highest probability of being cost-effective, because the level of uncertainty about the ICER is taken into account in the cost-effectiveness acceptability curve. Furthermore, two interventions with the same ICER can have different probabilities to be cost-effective because of differences in the distribution of costs and effects for different values of the input parameters. This is one of the reasons one should not base decisions solely on cost-effectiveness acceptability frontiers. Mean ICERs and CEACs are different ways of looking at a decision problem that is surrounded with uncertainty and offer complementary information (Claxton, 1999).

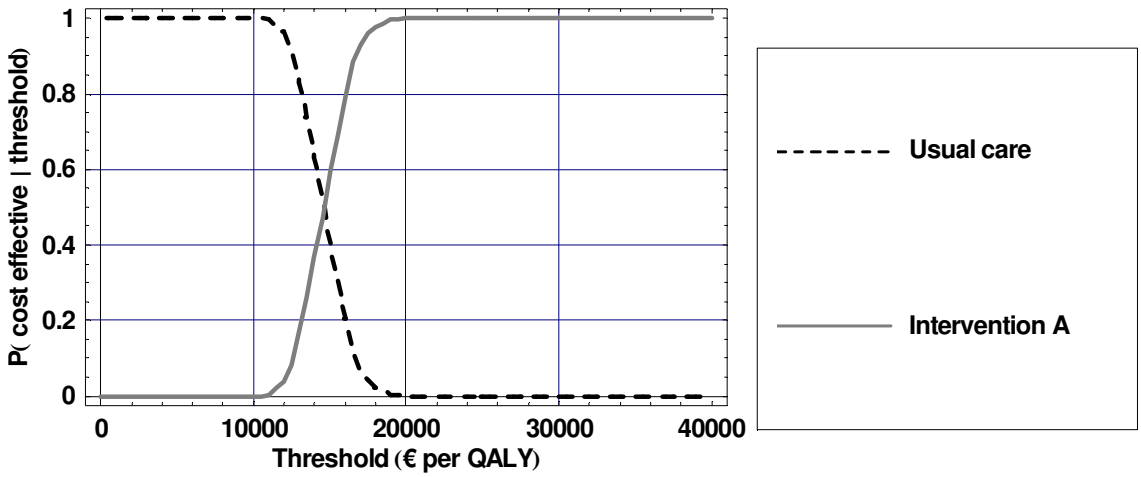

Figure 6.2: Example of a cost-effectiveness acceptability curve

The incorporation of uncertainty into cost-effectiveness analysis is not merely an academic exercise. The issue of uncertainty is closely related to real life decision making in the field of health care (Claxton et al., 2005). There is no such thing as making decisions without uncertainty since we never know for sure what future outcomes of current health policy will be. However, decisions inevitably have to be made under uncertainty and continuing with usual care is just as well a decision as deciding to change usual care. Therefore, the choice was made to explicitly incorporate uncertainty for some model input parameters in the presentation of the results in this part of the report. This is done as a first step in incorporating uncertainty in the presentation of results of economic evaluations performed at the RIVM.

7. The prevention of recurrent depression by maintenance cognitive behavioural therapy

7.1 Description of health problem and the intervention

In the Netherlands, the twelvemonth prevalence of major depression is estimated at 737,000 (i.e. 5.4% of those above 12 years of age). Depression is less prevalent in adolescents (3.8%), and elderly people (5.0%), as compared to *adults* between 18 and 65 years of age (5.7%). Each year almost 300,000 adults develop a major depression for the first time (De Hollander et al., 2006). Depression ranks fourth in the burden of disease list in the Netherlands (De Hollander et al., 2006) and the prevalence of depression is twice as high in women as in men. In 2003, the costs of care for depression (including the costs for dysthymia) were € 660 million (Slobbe et al., 2006).

The mean duration of an episode of depression is 6 months, the two-year risk of recurrence is 40%, and the lifetime risk of recurrence is even 70-80% (Meijer et al., 2006). These figures explain why depression is by a growing amount of experts considered as a chronic disease rather than an episodic disease currently. So, the treatment of depression should not only be aimed at the treatment of the specific episode, but also at the prevention of recurrences (Gilbody et al., 2006). This is why more and more long-term maintenance treatments are advocated. In this section the cost-effectiveness of maintenance Cognitive Behavioural Therapy (mCBT) is estimated. The calculations were based on a study by Vos and colleagues who evaluated the costs and effects of several treatment strategies for major depression (Vos et al., 2005). A 5-year maintenance treatment with CBT came to the fore as most cost-effective (varying from cost-saving to Aus$ 3,000/QALY).

CBT is a psychological treatment process that helps patients to correct false self beliefs that lead to depressed mood *and* behaviour (Rupke et al., 2006). CBT usually consists of several sessions with a therapist, either in groups or individually. The maintenance variant of CBT includes regularly (once or twice a year) booster sessions with the therapist for a period of five years.

The setting in which the costs and effects of mCBT were calculated is the Dutch general practitioner. The costs and effects of mCBT are compared to the costs and effects of usual care in this setting. The twelvemonth prevalence for depression diagnosed by the general practitioner is 363,000 (Westert et al., 2006). This is only half of the total prevalence in the Netherlands. Of the patients who are diagnosed by their GP as suffering from a major depression, 78,4% receive antidepressants, only 2,2% are referred to mental health care and 20% neither receives antidepressants nor is referred to mental health. (Westert et al., 2006).

7.2 Methodology

Major depression is a disease that is characterised by episodes with depressive symptoms and periods without depressive symptoms. Once in a depressed episode, the probability to recover declines as the length of the episode increases. Vice versa: once recovered, probabilities to relapse decrease as time elapses. Therefore, a Markov model was developed distinguishing depressed and non-depressed states in which recovery and relapse probabilities are dependent on the time spent in a state (see Figure 7.1).

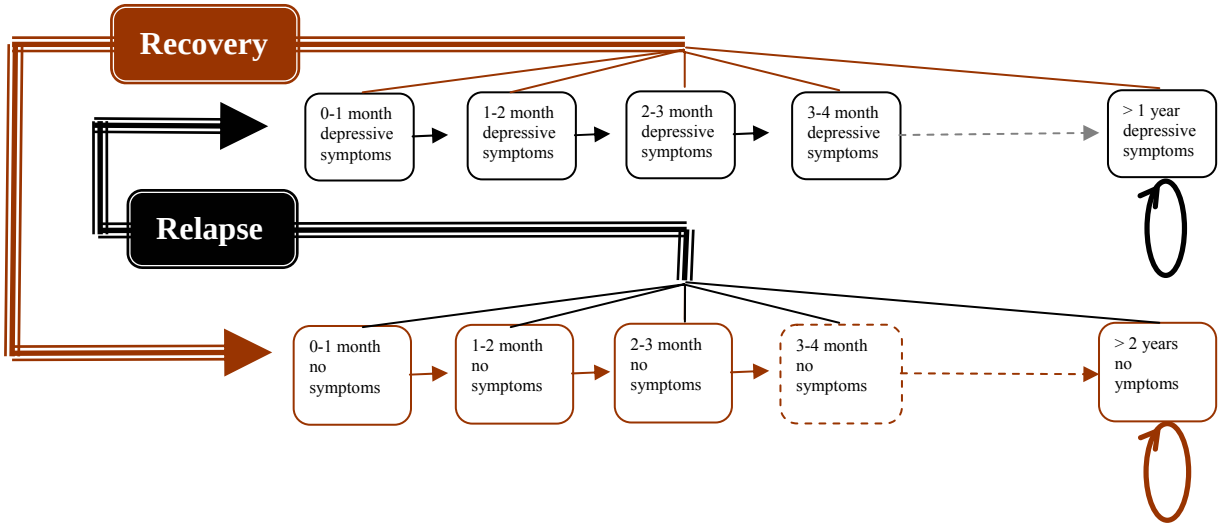

Figure 7.1: Schematic representation of the Markov model of depression

The Markov model allows simulating a cohort of people diagnosed with depression over time in cycles of four weeks. Thus, in every cycle a person with depressive symptoms has a probability to either recover or to remain depressed. Transition probabilities of the model were taken from the relapse and recovery curves presented by Vos et al., (Vos et al., 2004) and are displayed in Appendix 8. Since we had no empirical data on the initial distribution of all people diagnosed with depression by the GP over all model states, we generated this distribution by running the model for a cohort of persons just recovered from an episode (all persons have 0 - 3 weeks no depressive symptoms at baseline) for 30 years. After 30 years the distribution is in a so-called steady state which means that given the input parameters the distribution over the model states is stable. Since this steady state distribution is independent of the initial distribution over the model states we used this as our baseline distribution. The initial distribution over all possible states is displayed in Appendix 8.

The usual care scenario is determined by using the Second National Study of Dutch general practitioner (Westert et al., 2006). Patients diagnosed with a major depression contact their GP on average 4 times a year for depression. Of those contacts, 66.4% are consultations, 4.4% are visits by the GP and 29% are telephone contacts. The mean duration of a GP consultation is 15 minutes (Westert et al., 2006). On average 78.4% of the patients receive antidepressants. Of them 59.4% receive specific serotonine reuptake inhibitor (SSRI), 13% receive tricyclic antidepressants, 12.6% other antidepressants, 12% benzodiazepines anxiolytica and 3.1% benzodiapines sedative. On average 2.2% of the patients are referred to mental health care, such as RIAGG, psychiatrists and psychologists. Because of this small

percentage and the diversity in intensity of mental health care this subpopulation receives, we left this out of our calculation.

Table 7.1 displays estimated costs for usual care and the mCBT maintenance intervention**.** These costs were calculated by using a bottom-up method; first the intervention was outlined in detail to estimate the expecte resource use and secondly, this resource use was multiplied by standardized unit costs (Oostenbrink et al., 2000).

Table 7.1: Intervention costs per patient for mCBT and usual care (undiscounted, 2005 euros)

Scenario	Period and type of costs	Units	Unit price	Costs
mCBT	*Total costs year 1*			
	GP time	10	2,07	20,70
	Psychologist time	6*60	1,12	403,20
	Manual	1	12,85	12,85
	Total costs per year years 2, 3, 4 and 5			
	Psychologist time			
	minimum	1*60	1,12	67
	maximum	2*60		134
Usual care				
	Medication costs per month			
	Specific serotonine reuptake (SSRI) No6AB Paroxetine	59%	14 (15 tablets of 20mg)	17[a]
	Tricyclic antidepressants, No6AA Amitriptyline	13%	8 (15 tablets of 75 mg)	4[b]
	other antidepressants, No6AX Venlafaxine	13%	22 (10 tablets of 150 mg)	9
	benzodiazepines anxiolytica, No5BA Oxazepam	12%	8 (15 tablets of 50 mg)	2
	benzodiapines sedative, No5CD Temazepam	5%	9 (15 tablets of 20mg)	1
	Other costs per year			
	GP time	3*15	2,07	93,15
	GP time	1*5	2,07	10,35
	Telephone costs	1	0,04	0,04
	Telephone costs	5	0,03	0,15

[a] Calculated as 14 euro * 2 (for 30 days) * 1 (for 20 mg) * 59%

[b] Calculated as 8 euro * 2 (for 30 days) * 2 (for 150 mg) * 13%

In the cost calculation of mCBT, it was assumed that all sessions were individual sessions provided by a psychologist and that one manual was given to each patient. In the years thereafter, individual sessions were provided by a psychologist as well. In the usual care scenario, antidepressants were included. The medication costs per patient were taken from a medication website from the Dutch Organisation for Health Care Financing (CVZ, 2006). For the calculation per type of antidepressive medication, the medicine was taken that was prescribed most in the GIP database (GIP, 2003). The GIP database is a database in which the

medication use of the Dutch population can be found. Assumed are average dosages of 150 mg for TCA, 20 mg for SSRIs and 150 mg for other antidepressants. Because not all the GP contacts under usual care are consultations, it is assumed that 66% of the 4 contacts were consultations (is 3) and 30% of the contacts were telephone contacts (is 1). As mentioned before the duration of a consultation was on average 15 minutes. Furthermore, an average duration of a telephone contact of 5 minutes is assumed.

Costs and effects in terms of QALYs can be calculated with the model by coupling costs and disability weights to the states distinguished in the model. In the model it is assumed that quality of life equals 1 if not depressed and (1- 0.46) if depressed but not treated (Kruijshaar et al., 2003). Treatment of major depression affects quality of life during an episode and the risk of relapse when recovered from the episode. To estimate effects of interventions, different scenarios are run with the model in which in the intervention scenario transition relapse probabilities are decreased and quality of life weights during depressive episodes are increased. Generally, effects of interventions are not measured in terms of quality of life but in terms of depression severity measured with depression specific scales. To translate effects on depression severity to effects on quality of life we followed the same approach as Vos and colleagues (Sanderson et al., 2004). They used a conversion factor to translate effects measured in standard deviations on depressive specific measurement scales to effects on disability weights which is derived using a generic quality of life profile. In the usual care scenario, it is assumed that there is a lag to treatment, before a patient with depressive symptoms contacts the GP and receives treatment. In the mCBT there is no lag to treatment since it is assumed that all persons start with mCBT immediately. Improvements in quality of life occur once one starts with treatment. Furthermore, it is assumed that effects due to treatments only accrue to those who adhere to treatment.

Incremental cost-effectiveness ratios (ICER) were expressed in euro per QALYs gained. To reflect the uncertainty inherent in the estimation of most model parameters, probabilistic sensitivity analysis was carried out. Costs were discounted at 4.0% and effects at 1.5%, reflecting current Dutch standards. With PSA, uncertainty in the input parameters is addressed and reflected in the model output, the ICER (see Section 6.2 for explanation). In Table 7.2, the distributions used in the PSA are displayed. ICERs were estimated for two different populations: a population just recovered from a depressive episode and a mixed population in which an initial distribution over all model states is estimated (see Appendix 8). The latter population is a better reflection for the current population of people diagnosed with major depression in the GP, since some of them will be in a depressive episode for a while and some have been recovered. Table 7.2 summarizes the assumptions used to estimate the costs and effects of usual care and mCBT in the Dutch GP setting.

Table 7.2: Summary of assumptions and input data usual care and mCBT scenario

	Usual care: *Patients diagnosed with a major depression visit their GP on average 4 times a year for depression: 80% receive antidepressants, 20% neither receives antidepressants nor is referred to mental health.*	**mCBT:** *Patients known to have had a major depressive episode in the past visit their GP once (but not during a depressive episode) to be refererd to a CBT therapist. mCBT consists of 6 sessions in the first year and 4-8 booster sessions in the following 4 years.*
Target population	All persons diagnosed with major depression by GP*	All persons diagnosed with major depression by GP
Fixed parameters		
Discount rate	4% costs and 1.5% effects	4% costs and 1.5% effects
Time horizon	5 years	5 years
Transition probabilities 'no care'	Appendix 8	Appendix 8
Intervention costs	Medication costs per month: € 40	Intervention costs in the first year: € 437
Stochastic parameters		
Intervention costs	GP time[a]: Beta distribution (alfa=5; beta=5)*4	Number of booster sessions[a]: Beta distribution (alfa=5; beta=5) +1
Effect size (ES) measured in standard deviations	ES antidepressant drugs: Normal distribution Mean: 0.55 SD: (0.40-0.70)/(2*1.96)	ES mCBT: Normal distribution Mean: 0.77 SD: (0.44-1.10)/(2*1.96)
Change in Disability weight per unit ES	Uniform distribution 0.139-0.172	Uniform distribution 0.139-0.172
Lag to treatment	Triangular distribution: 0.1 or 2 cycles (4 weeks)	No lag to treatment
RR relapse	Lognormal distribution Mean: Log[0.416] SD: Log[(0.312-0.555)/(2*1.96)]	Lognormal distribution Mean: Log[0.437] SD: Log[(0.394-0.485)/(2*1.96)]
Adherence	Uniform distribution 0.5-0.73	Uniform distribution 0.5-0.81

[a] Used because of lack of data

[b] Used because of lack of data

*The 2.2% which are referred to mental health are left out of the analysis

7.3 Results

Figure 7.2 displays cumulative differences in costs and effects (both discounted) of mCBT compared to the Dutch usual care in a GP setting for one hypothetical patient for a period of five years for different values of the input parameters as specified in Appendix 8.

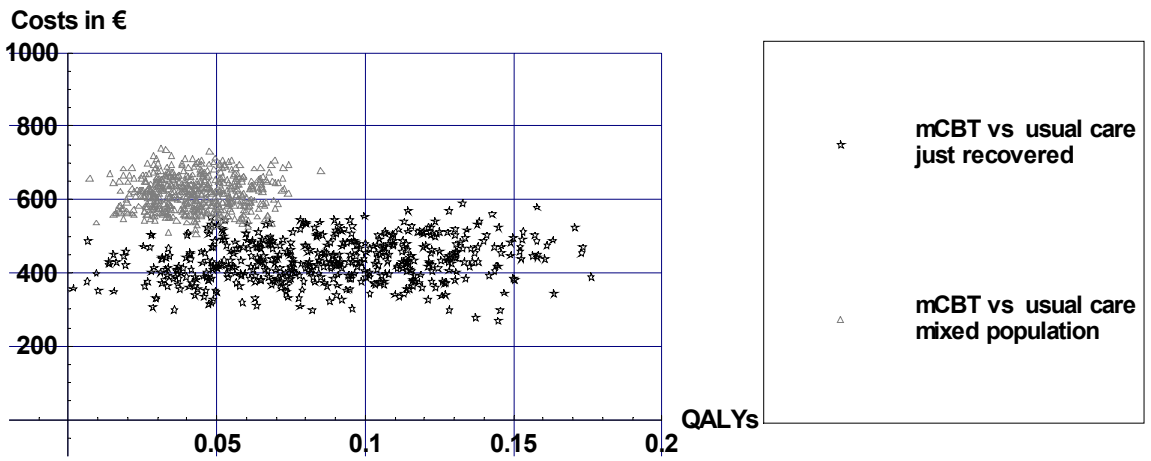

Figure 7.2: Incremental costs and effects mCBT compared to usual care per person

Figure 7.2 shows that if someone who has just recovered from a depressive episode receives mCBT instead of usual care he/she gains on average about 0.10 QALY over a period of five years at an additional cost of about € 500 resulting in an average cost-effectiveness ratio of € 5000 per QALY gained. In the mixed population, the health gains are somewhat lower and a patient on average gains 0.05 QALY over a period of 5 years at higher costs resulting in a mean ICER of € 15,000 per QALY gained. The health gains are lower than in a cohort of people just recovered from an episode since most health gains can be achieved after recovery due to improved risk of relapse. Table 7.3 displays estimates of total incremental costs and effects of mCBT in the mixed population in the GP setting (363,000 persons).

Table 7.3: Estimates of total incremental costs and effects of mCBT compared to usual care in the mixed population and their 95% confidence interval (between brackets), for a five year period

	mCBT in mixed population
QALYs (* 1,000)[a]	15 (8-23)
Costs (* € 1,000,000) [b]	223 (192 -254)

[a] Discounted with 1.5%
[b] Discounted with 4%

Figure 7.3 displays the cost-effectiveness acceptability curves (CEAC) for mCBT and usual care in a population just recovered from a depressive episode. A CEAC displays the probability that an intervention is cost-effective for values of the threshold i.e. monetary value of a QALY.

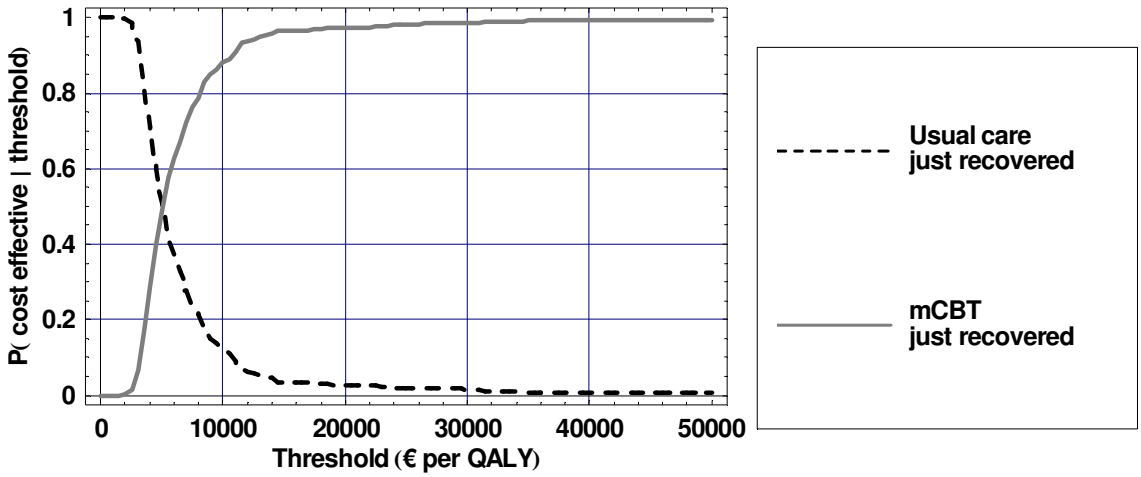

Figure 7.3: Cost-effectiveness acceptability curve for a population just recovered from a depressive episode

Figure 7.4 displays a CEAC for the mixed population.

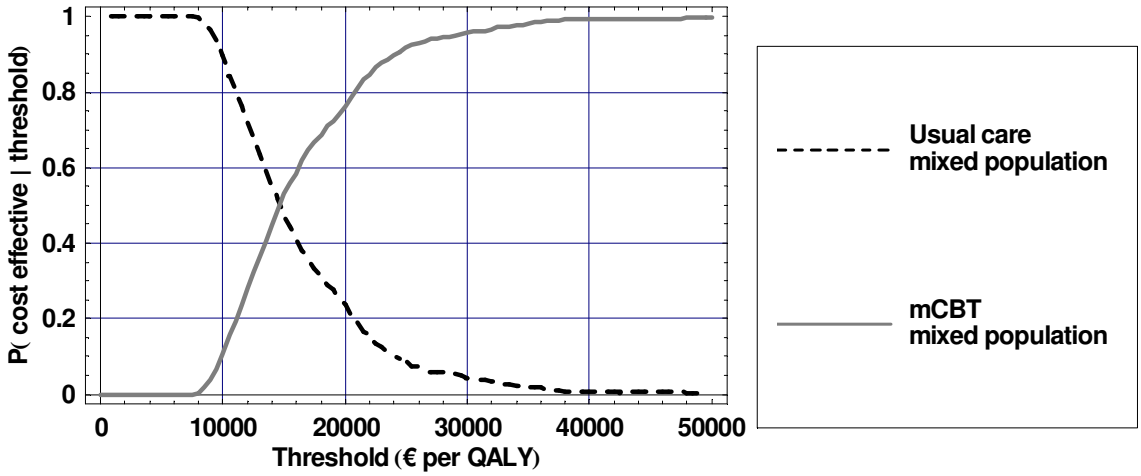

Figure 7.4: Cost-effectiveness acceptability curve for a mixed population

What can be derived from Figures 7.3 and 7.4 is that the probability that mCBT is more cost-effective than usual care increases as the threshold increases. If a threshold of

€ 20,000 per QALY is taken, mCBT has a high probability to be cost-effective, both in the mixed population and in the population just recovered. However, as we will elaborate on in the discussion, not all uncertainty is taken into account.

7.4 Conclusions on cost-effectiveness of intervention

The modelling study showed that health gains can be achieved at a relatively low cost if the GP refers persons diagnosed with major depression to mCBT instead of prescribing anti-depressive medication. Both in a cohort of people just recovered from a depressive episode and in a mixed population, the ICERs remain below the threshold of € 20,000 per QALY gained. This is mainly the result of a longer sustained period of risk reduction for recurrence. This conclusion should however be interpreted with caution, since a lot of parameters in the model are based on international studies while some important model parameters, like adherence to treatments, should preferably be based on Dutch data. As in any modelling study, some simplifying assumptions were made. One of the most important assumptions was that there was no modeling of heterogeneity of patients. Of course, people diagnosed with depression differ in the severity of their depressive symptoms and in their risk on recurrence and recovery. Furthermore, although we did take into account uncertainty around a lot of model parameters, uncertainty around some crucial parameters could not be addressed. Additional uncertainty may influence both estimates of the mean cost-effectiveness ratio and the decision uncertainty as displayed in the cost-effectiveness acceptability curves. To minimize uncertainty, further research should be done on the following issues:

- Uncertainty around relapse after recovery from a depressive episode and recovery once in a depressive episode;
- Adherence to treatments within the Netherlands;
- Estimation of intervention effects on quality of life.

An additional important result is that mCBT treatment of the whole group of persons with major depression by the GP is probably less cost-effective than persons just recovered from an episode. The ratios are somewhat higher compared to the study by Vos and colleagues (Vos et al., 2005), which focused on persons just recovered from a depressive episode, even though costs were discounted at a higher rate and effects at a lower rate. This has to do with the fact that in the Dutch GP setting more persons already receive evidence-based treatments (about 80% receive antidepressants which also reduces symptoms and improves the relapse risk) than in the study by Vos et al. (about 60%). Secondly, antidepressants are relatively cheaper in the Netherlands compared to the costs of cognitive behavioural therapy. Third, Vos et al. (2005) took into account the effects of treatments on the risk of suicide. Due to lack of data, effects of treatments on suicides were not taken into account. Of course, health gains would increase if mCBT decreases the risk of suicide. However, taking into account effects on suicide would imply a longer time horizon for the interventions and taking into account medical costs in life years gained.

8. The prevention of chronic diseases by diet and pharmacologic treatment of obesity

8.1 Description of the health problem and the intervention

In the Netherlands, one in every ten individuals is obese (i.e. BMI≥30 kg/m^2). Obesity entails an increased risk for type 2 diabetes, high blood pressure, high cholesterol, heart disease, cancer, musculoskeletal disorders, respiratory problems, and psychosocial problems. Moderate overweight (25<BMI<30 kg/m^2) and obesity yearly cause 40,000 cases of heart disease, type 2 diabetes, and cancer, and circa 7% of all mortality. It is estimated that the health problems due to overweight cause a loss of 215.000 DALYs each year (De Hollander et al., 2006).

Successful treatment of obesity (weight loss) will reduce the increased risk for these chronic diseases, and will thus prevent much burden of disease. The treatment should be aimed at a modest weight loss (5-15%) which has to be sustained in the long term (Zelissen and Mathus-Vliegen, 2004). Such a modest, sustained weight loss reduces risk factors and morbidity in obese patients. Treatment options include lifestyle programmes (e.g. diet therapy, exercise programme, behavioural therapy), pharmacological treatment, or surgery. Currently there are no guidelines for the treatment of obesity in the Netherlands. International guidelines state that the treatment of obesity should focus on producing substantial weight loss over a prolonged period of time (NHLBI, 1998). This treatment should focus on altering dietary and physical activity patterns. As part of a comprehensive weight loss programme, pharmacological treatment is recommended for patients with obesity (NHLBI, 1998). It is emphasized that weight loss drugs should never be used without concomitant lifestyle changes. The Dutch Health Council recommended an integrated approach, i.e. a combination of lifestyle programmes and pharmacologic treatment (Health Council of the Netherlands, 2003).

The most frequently used weight loss drugs are Orlistat and Sibutramine. Many studies have shown that the pharmacologic treatment of obesity (i.e. drugs in combination with lifestyle changes) is effective in achieving a modest weight loss (Li et al., 2005). Several economic evaluations reported that pharmacological treatment of obesity is cost-effective compared to lifestyle changes only (Vijgen et al., 2005). This study aimed to estimate the cost-effectiveness of the prevention of chronic disease by pharmacological treatment of obesity in combination with a diet in the Netherlands. Costs and effects of a diet only intervention and diet in combination with Orlistat for one year are compared to the cost and effects of no care. It was chosen to use no care as comparator since the Second National Study of Dutch general practitioner showed that primary care patients diagnosed with obesity receive pharmacological treatment in 22% of the cases, and 5% are referred to a dietician (Westert et al., 2006). All other patients receive no obesity treatment, or only informal lifestyle advice of low intensity.

8.2 Methodology

Orlistat in combination with a diet was compared to a diet alone and no care at all to compute incremental cost-effectiveness ratios. The target population were all Dutch people between 20 and 70 years with a BMI>30 that receive no care at all for their obesity (80% of the obese population). In the diet only intervention, everybody in the target population receives a low-calorie diet, while being counseled by a dietician. In the diet + Orlistat intervention everybody receives pharmacologic treatment (Orlistat) in addition to a low-calorie diet and counselling by a dietician. Those who do not respond to the treatment (i.e. those who lose <5% of their weight within the first three months) discontinue Orlistat treatment (circa 50%) (Li et al., 2005).

Table 8.1 displays the intervention costs as calculated for the Orlistat intervention. These costs were calculated by using a bottom-up method; first the intervention was outlined in detail to estimate the resource use and thereafter, this resource use was multiplied by standardized unit costs (Oostenbrink et al., 2000). In the cost calculation it was assumed that those who do not respond to the Orlistat treatment (50%) visit only two times the dietician, and the patients who receive Orlistat for one year visit the dietician every three months. A food diary was given to each patient. The medication costs per patient were taken from the Pharmacotherapeutic Kompas. An Orlistat tablet has to be taken three times a day during a meal.

Table 8.1: Intervention costs per patient (2005 euros)

Period and type of costs	Units	Unit price	Costs
Total costs year 1			
GP time	10-20	2,07	20,70-41,40
Dietician time	120-240	0,85	102-204
Manual	1	12,85	12,85
Orlistat (3 tablets per day)			
Minimum only 3 months	50%	45 (45 tablets of 120 mg.)	270
Maximum for 12 months	50%		1080

Intervention effects of a low-calorie diet (Finer, 2001) and of diet in combination with Orlistat on weight after one year were taken from the international literature (Li et al., 2005). These were then translated into long term weight loss by assuming that about 20% of the weigth loss after one year can be maintaned in the long run (Anderson et al., 2001).

The health gains of long term weight loss were estimated using the RIVM Chronic Disease Model (CDM) (Hoogenveen et al., 1998; Van Baal et al., 2005; Van Baal et al., 2006d). The CDM is a dynamic population model that describes the life course of cohorts in terms of transitions between risk factor classes and changes between disease states over time. Body weight is modeled in three classes using Body Mass Index (BMI) as indicator: BMI<25 (normal weight), 25≤BMI<30 (overweight), BMI ≥30 (obesity). To estimate differences in QALYs and lifetime health care costs due to the intervention, effects of long term weight loss were translated into differences in obesity prevalence. This was done by subtracting the long

term weight loss achieved through the intervention from the weight distribution of the target population and then comparing the differences in obesity prevalence. This was done using data on the BMI distribution from the NS2 study (Westert et al., 2006). QALYs gained were then calculated by multiplying differences in obesity prevalence by the difference in health-adjusted life expectancy between an obese person and an overweight person (age and sex specific since all parameters and variables in the CDM are specified by gender and age). Analogously, differences in lifetime health care costs are estimated with CDM. To compute health effects in terms of QALYs, data from the Dutch Burden of Disease Study (Stouthard et al., 1997) are used in the CDM (Van Baal et al., 2006c; Van Baal et al., 2006d; Van Baal et al., 2005). Health care costs in the CDM are based on the Dutch Costs of Illness study (Slobbe et al., 2006). Cost-effectiveness was evaluated from a health care perspective and included intervention costs and differences in lifetime medical costs (Van Baal et al., 2006b). Effects and costs were discounted at 1.5% and 4.0% annually, respectively. The time horizon for assessing future health impact was 100 years since this allows the target population to become extinct in order to estimate lifetime effects. Table 8.2 summarizes the assumptions and input data used.

Table 8.2: Summary of assumptions and input data

	Diet only: *Low calory diet for everybody in target population, in combination with counselling by a dietician*	**Diet + Orlistat:** *Low calory diet for everybody in target population, in combination with counselling by a dietician, 50% receives Orlistat for 3 months, 50% receives Orlistat one year*
Target population	all Dutch people between 20 and 70 years with a BMI>30 that receive no care at all for their obesity (80% of the population BMI>30) 1.1 million people	all Dutch people between 20 and 70 years with a BMI>30 that receive no care at all for their obesity (80% of the population BMI>30) 1.1 million people
Deterministic parameters		
Discount rate	4.0% costs and 1.5% effects	4.0% costs and 1.5% effects
Time horizon	100 years	100 years
*Average gain in QALYs per person**	1.45	1.45
*Average difference in lifetime health care costs per person***	€ 5000	€ 5000
Stochastic parameter		
Intervention costs	GP time Dietician time	GP time Dietician time
Weight loss after one year diet in kilogram (Finer, 2001)	Normal distribution Mean: 3.2 SD: 0.54	Normal distribution Mean: 3.2 SD: 0.54
Weight loss after one year Orlistat in kilogram (Li et al., 2005)		Normal distribution Mean: 2.7 SD: 0.31
Succesfull weigth loss maintenance(Anderson et al., 2001)	Normal distribution Mean: 0.23 SD: 0.015	Normal distribution Mean: 0.23 SD: 0.015

* discounted at 1.5%

** discounted at 4%

8.3 Results

Figure 8.1 displays a cost-effectiveness plane of diet and diet + Orlistat compared to usual care for the average person receiving the intervention for different values of the input parameters as specified in Table 8.2.

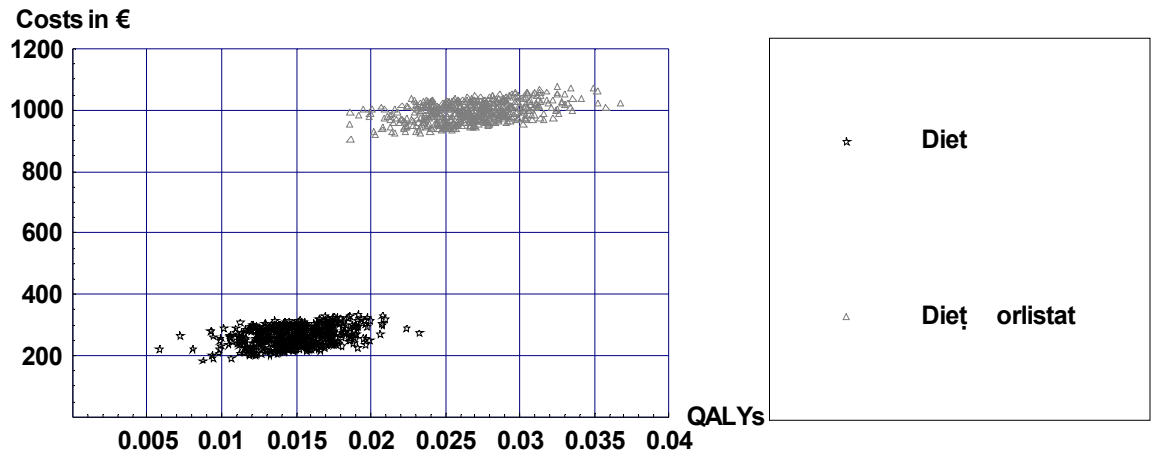

Figure 8.1: Incremental costs and effects of diet and diet+ Orlistat compared to usual care for the average person receiving intervention

What can be seen from Figure 8.1 is that diet alone results in less health gains than diet in combination with Orlistat. Costs per QALY gained are € 18,000 for diet compared to usual care (no care) and € 62,000 of diet plus Orlistat compared to diet only. Table 8.3 displays incremental QALYs and health care costs for the target population.

Table 8.3: Estimates of total costs and effects of diet and diet in combination with Orlistat for target population and their 95% confidence interval (between brackets)

	Diet only	**Diet in combination with Orlistat**
QALYs (* 1000)[a]	17 (11-22)	30 (24-38)
Costs (* € 1,000,000)[b]	300 (235-365)	1130 (1060-1200)

[a]Discounted with 1.5% [b]Discounted with 4%

Whether diet or diet + Orlistat can be called cost-effective depends on how QALYs are valued in monetary terms. Figure 8.2 displays the CEACs for usual care, diet and diet + Orlistat. What can be derived from Figure 8.2 is that for low monetary values placed on a QALY neither diet nor diet + Orlistat is probably cost-effective. For values places on a QALY between € 15,000 and € 65,000 diet alone is probably most cost-effective. For values higher than € 65,000 diet + Orlistat is probably most cost-effective.

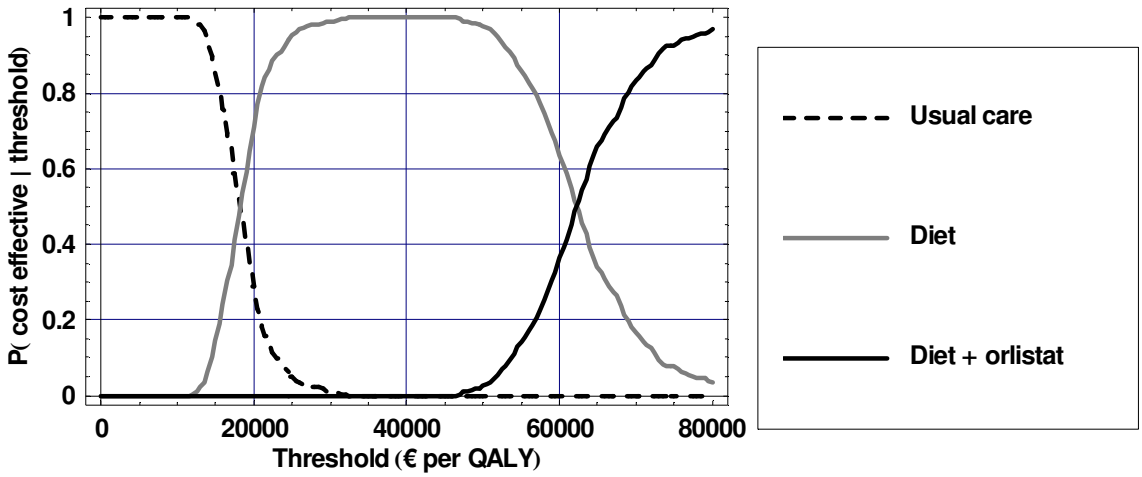

Figure 8.2: Cost-effectiveness acceptability curves for usual care, diet and diet in combination with Orlistat

8.4 Conclusions on cost-effectiveness of intervention

Compared to previous studies, this modelling exercise reveals a higher cost-effectiveness ratio for the treatment of obesity through a diet in combination with Orlistat. One of the explanations for the different results is the difference in the methods used to calculate QALYs. A study by Hertzman (2005) used a much shorter time horizon (5 years) and assumed a direct effect of decreases in BMI on improvements in quality of life based on a study by Hakim et al. (2002). They assumed improvements in QOL during the first years after the intervention. In the model, improvements are assumed in quality of life through a reduced risk on disease incidence. The methodology accounts for much smaller gains in quality of life during normal life years (i.e. life years that would have also been lived without the intervention) (Van Baal et al., 2006d). Furthermore, the effect that quality of life generally decreases with advancing age was taken into account. This is important, since obviously the life years gained occur at high ages. This approach mostly resembles the approach used by Roux et al. (2006) in the sense that a lifetime perspective was used. They tracked lifetime costs and took into account the same amount of long term weight loss maintenance. However, they did not take into account effects of diseases in life years gained on quality of life. This may explain the large differences between costs per life year gained and costs per QALY gained they found.

Ideally, BMI should be modelled as a continuous risk factor which allows a direct computation of health gains due to weight changes. However, in the model three different BMI classes were used with average relative risks computed using the BMI distribution within these classes in the Netherlands. This means that health gains for persons with extreme obesity were underestimated, and that health gains for persons with moderate obesity were overestimated. To what extent this approach results in biased estimates of health gains and therefore in biased estimates of the ICER is difficult to hypothesize. Another crucial assumption was that weight loss maintenance was equal in both diet and diet plus Orlistat intervention. There is some evidence that weight loss maintenance is higher in

pharmacological treatment (Mathus-Vliegen, 2005) which would improve the cost-effectiveness of pharmacological treatment of obesity relative to a diet only.

Since cost-effectiveness analysis requires assumptions about the effectiveness on interventions on BMI in the long term, the outcomes of the scenarios presented in this study should be interpreted with caution. In this study, it was assumed that 20% of the weight loss was maintained in the long run. If this relapse was not taken into account, costs would be substantially lower: € 8,000 per QALY gained for diet only and € 24,000 per QALY gained for diet in combination with Orlistat. It has been shown that longer and active follow up can prevent weight regain (Saris, 2001). However, this would involve additional costs and thus it is difficult to hypothesize to what extent this would influence cost-effectiveness.

9. Conclusion and discussion on part B of this report

In the former report on economic evaluations of preventive interventions evidence was presented from international cost-effectiveness analyses on the cost-effectiveness of prevention of recurrent depression by maintenance cognitive behavioural therapy (mCBT), and the prevention of chronic diseases by pharmacologic treatment of obesity (Vijgen et al., 2005). Both these interventions appeared to be cost-effective in a foreign setting. By modelling both interventions within a Dutch setting and using in the case of obesity prevention a different modelling approach, a few important lessons can be learned. First of all, our results demonstrate that both interventions have less favourable cost-effectiveness ratios than presented so-far in the literature. In case of mCBT, the ratios still remain below the threshold of € 20,000 employed in this study. In case of Orlistat treatment, the ratio was more than € 60,000. However, a low calorie diet appeared to be more cost-effective than pharmacological treatment of obesity with a mean ICER of € 18,000 per QALY gained. Differences in the cost-effectiveness of mCBT can partly be explained by the setting of the Dutch GP that was chosen. Since already a lot of people diagnosed by the GP with major depression receive evidence based care through antidepressants, the room for potential health gains is relatively limited. However, the present results suggest that even in this setting, health gains can be achieved at a low cost if the GP redirects persons with depressive symptoms to mCBT instead of prescribing medication. An important new insight is that mCBT yields most health gains at a lower price in people just recovered from a depressive episode. This means that if mCBT would be offered to the current population of depressive persons in the GP setting, health gains would be lower. It should be noted that in both modelling studies, additional research is needed that can improve estimates of cost-effectiveness considerably. In the modelling study of mCBT mainly foreign data were used to fill parameters of the model. It deserves recommendation to incorporate more Dutch data into the model. Furthermore, more research should be devoted to relapse and recovery of persons diagnosed with depression. In case of weigth loss interventions, a crucial parameter that needs more research is long term weigth loss.

A health-economic evaluation from the health care perspective was performed. It concentrated on effects of interventions on health and health care costs and compared these with intervention costs. This may be relevant information for the health care decision maker, who may be primarily concerned with health care costs (Brouwer et al., 2006; Van Baal et al., 2006a). We did not present effects on productivity costs and did not take into account effects on informal care. Taking this into account, in turn, would suggest a societal perspective to be used in cost-effectiveness analysis to demonstrate the broader societal costs and benefits from the interventions (Brouwer and Koopmanschap, 2000). Such a broader perspective is normally advocated in economic evaluations, since it gives a complete picture of welfare changes in society associated with some intervention (Meltzer, 1997). A next step, therefore, would be to assess the cost-effectiveness of these interventions from a societal perspective.

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Chapter 3: Results: newly identified preventive interventions

Chapter 3.1: Screening for group B streptococcal infections

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List of abbreviations

aP	acellular pertussis (vaccine)
CBA	cost benefit analysis
CDC	Center for disease control and prevention
CEA	cost-effectiveness analysis
CEAC	Cost Effectiveness Acceptability Curve
CIN-3	cervical intraepithelial neoplasia, pre-cancerous lesions of the cervix
CUA	cost utility analysis
CWFP	Community water fluoridation programme
DALY	Disability adjusted life years
DM	diabetes mellitus
DMFT	number of Decayed, Missing or Filled teeth
DTP	Difterie, Tetanus, Polio
DTP-IPV	diphtheria, tetanus, pertussis and polio
ECU	European Currency Unit
EOD	early onset disease
EUROCAT	European registration of congenital abnormalities and twins
GBS	Group beta streptococcus
HBsAG	Hepatitis B Surface antigene
HBV	Hepatitis B virus
HFA	Health for all
Hib	Haemophilias influenza b
HPV	human papilloma virus
IAP	intrapartum antibiotic prophylaxis
IDDM	Insulin Dependent Diabetes Mellitus
IGT	Impaired Glucose Tolerance
ICER	Incremental Cost Effectiveness Ratio
LS	Lifes Saved
LYG	Life Years Gained
LYS	Life Years Saved
MMR	Measles, Mumps, Rubella
NIDDM	Non Insulin Dependent Diabetes Mellitus
NIP	National Immunization Programme
NTD	Neural tube defect
NVI	Nederlands Vaccin Instituut (Dutch Vaccine Institute)
NVK	Nederlandse Vereniging van Kinderartsen
NVOG	Nederlandse Vereniging voor Obstetrie en Gynaecologie
PSA	Probabilistic Sensitivity Analysis
QALY	Quality adjusted life year
PCR	polymerase chain reaction
ppm	parts per million
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised Clinical Trial
RR	Relative risk
RV	Rotavirus
Tdap	diphtheria, acellular pertussis and tetanus vaccination formulation for adolescents and adults

VZV	Varicella zoster virus
WHO	World Health Organisation

Appendix 1: Questions regarding the identification of preventive interventions

General approach:

- Send an e-mail to people from inside the RIVM with an explanation of the interviews and ask for participation (21/2 send by Jantine)
- Make an appointment (reserve a room)(20/2 to 3/3)
- Send the questions two days before the interview and the list with already included interventions (and previous interview if necessary)
- If the person was interviewed in 2002 as well, read the previous interview. Some questions can be excluded then (with #) or reformulated (with *).

Questions

1. What is your expertise?#
2. Have you been part of an evaluation study (from 2003*) concerning preventive interventions yourself?
3. If question is answered with yes: Were economic aspects examined in that study?
4. Do you know published economic evaluations of prevention in the literature? Think of grey literature (not peer-reviewed) as well, and of research reports.
5. Do you know Dutch research (since 2003*) that focus on economic effects of prevention? Foreign studies can be mentioned here as well.
6. Are there preventive interventions of which you think they are cost-saving or otherwise interesting from an economic point of view? Although no evidence base is known.
7. Which other persons from the RIVM should we interview?
8. Which other persons from outside the RIVM should we interview?

Appendix 2: Overview of potentially cost-effective preventive interventions

No.		Source	Remark	Included in report
1	Intensive blood pressure control in type 2 diabetic patients	Dirkmaat et al. (2003) [a]	Included in guidelines	
2	Intensive blood glucose control in diabetic patients with overweight	Dirkmaat et al.	Included in guidelines	
3	National Immunization Programme	Dirkmaat et al.	Implemented	
4	Prevention of coronary heart diseases by diminished consumption of saturated fats	Dirkmaat et al.	Not enough good studies	
5	Influenza vaccination (elderly)	Dirkmaat et al.	Implemented	
6	Influenza vaccination (healthy working adults)	Dirkmaat et al.		Update
7	Fluoridation of drinking water	Dirkmaat et al.		Update
8	Hepatitis A vaccination (selected groups workers)	Dirkmaat et al.	Interventions not comparable	
9	HIV prevention (needle exchange programme)	Dirkmaat et al.	Implemented	
10	Folic acid fortification to prevent neural tube defects	Dirkmaat et al.		Update
11	PKU/CHT screening	Dirkmaat et al.	Implemented	
12	Varicella vaccination	Dirkmaat et al.		Update
13	Prevention accidental falls among the elderly	Dirkmaat et al. and workshop	Interventions not comparable	
14	Screening pregnant women on syphilis	Dirkmaat et al.	Implemented	
15	Chlamydia screening	Dirkmaat et al. and Vijgen et al. (incl) and workshop	Update not necessary [b]	
16	Interventions for smoking cessation through the GP	Dirkmaat et al. and workshop		Update
17	Pneumococcal vaccination in the elderly	Dirkmaat et al. and workshop		Update
18	Breastfeeding promotion	Dirkmaat et al.	Not enough good studies	
19	Prevention of sudden cardiac death by using automatic external defibrillators	Vijgen et al. (2005) (incl) [c]	Update not necessary	
20	Prevention of hip fractures by using external hip protectors	Vijgen et al. (incl)	Update not necessary	
21	Prevention of head injuries in children by bike helmet usage	Vijgen et al. (incl)	Update not necessary	
22	Prevention of recurrent depression by treatment	Vijgen et al. (incl)	Update not necessary	Modelling
23	Abdominal aortic aneurysm (AAA) screening	Vijgen et al. (incl)	Update not necessary	
24	Prevention of blindness by retinopathy screening in diabetic patients	Vijgen et al. (incl)	Update not necessary	
25	Prevention of cervix cancer by HPV screening combined with cervical cytology	Vijgen et al. (incl)	Update not necessary	

No.		Source	Remark	Included in report
26	Prevention of chronic diseases by treatment of obesitas (medication and lifestyle)	Vijgen et al. (incl)	Update not necessary	Modelling
27	Prevention of recurrent myocardial infarct by heart revalidation	Vijgen et al. (incl)	Update not necessary	
28	Constructing bicycle- and footpaths	Vijgen et al. (excl) [d]	Not enough good studies	
29	Prevention of overweight by lifestyle advises of nurse practitioners	Vijgen et al. (excl)	Not enough good studies	
30	Prevention of overweight by tax measures on food (snack-tax)	Vijgen et al. (excl)	Not enough good studies	
31	Screening on coronary heart diseases in settings	Vijgen et al. (excl)	Many different settings	
32	Prevention of coronary heart diseases by folic acid fortification	Vijgen et al. (excl)	Not enough good studies	
33	Familial breast cancer screening	Vijgen et al. (excl)	Not enough good studies	
34	Prevention of chronic low back pain through back-schools	Vijgen et al. (excl) and workshop	Interventions not comparable	
35	Prevention of osteoporoses by supplements or lifestyle advice	Vijgen et al. (excl)	Not enough good studies	
36	Screening colon cancer	Workshop	Implemented	
37	Injury prevention (elderly)	Workshop	See: prevention accidental falls among the elderly (no. 13)	
38	Lifestyle programmes diabetic type 2 patients	Workshop	Included in guidelines	
39	Folic acid supplementation for women capable of becoming pregnant	Canadese Report (2004) [e]	Not enough good studies	
40	Urine culture in pregnant women	Can. Report	Not enough good studies	
41	Ocular prophylaxis in newborns (ophtalmia neonatorum)	Can. Report	Not enough good studies	
42	Haemoglobin electrophoresis in high-risk neonates	Can. Report	Not enough good studies	
43	Eye exam in infants (amblyopia)	Can. Report	Implemented	
44	Hearing assessment using parental questioning and clap test in infants	Can. Report	Will be implemented as of January 1st 2007	
45	Supervised period of observation in newborns with clinically detected DDH (developmental dysplasia of the hip)	Can. Report	Not enough good studies	
46	Home visitation by nurses during perinatal period through infancy for first-time mothers of low SES, single parents or teenaged parents.	Can. Report	Not enough good studies	
47	Day care or preschool programmes for disadvantaged children	Can. Report	Not enough good studies	
48	Counselling to reduce home risk factors with parents of infants	Can. Report	Not enough good studies	
49	Universal hepatitis B vaccination	Can. Report		New

No.		Source	Remark	Included in report
50	Urine dipstick in adults with insulin dependent diabetes mellitus (progressive renal disease	Can. Report	Not enough good studies	
51	Medical treatment for diagnosed depression in high risk population (suicide)	Can. Report	Not enough good studies	
52	Voluntary HIV antibody screening in high-risk populations	Can. Report and interview	Implemented	
53	Mantoux tuberculin skin test in high-risk groups (TBC)	Can. Report	Implemented	
54	Assessment and follow-up based upon caregiver or informant description of decline in elderly (cognitive impairment)	Can. Report	Not enough good studies	
55	Noise control and hearing protection in general population (hearing impairment)	Can. Report	Not enough good studies	
56	Increase price of alcohol products (prevention of alcohol abuse and misuse)	Can. Report	Not enough good studies	
57	Legal drinking age (prevention of alcohol abuse and misuse)	Can. Report	Not enough good studies	
58	School-based alcohol education programmes (prevention of alcohol abuse and misuse)	Can. Report	Not enough good studies	
59	Community education campaign (prevention of alcohol abuse and misuse)	Can. Report	Not enough good studies	
60	School-based physical education (increase physical activity)	Can. Report	Not enough good studies	
61	Community education campaigns (increase physical activity)	Can. Report	Not enough good studies	
62	Providing social support in community settings (increase physical activity)	Can. Report	Not enough good studies	
63	Creating or improving access to places for physical activity (increase physical activity)	Can. Report	Not enough good studies	
64	CMV (mandatory or universal screening for disease with effective prophylaxis for infant)	Can. Report	Not enough good studies	
65	GrpB Strep (mandatory or universal screening for disease with effective prophylaxis for infant)	Can. Report and interview		New
66	Health education toxoplasmosis (mandatory or universal screening for disease with effective prophylaxis for infant)	Can. Report	Not enough good studies	
67	Reducing costs of higher education to improve access to higher education	Can. Report	Long-term effectiveness	
68	HIV screening immigrants	Can. Report	Implemented	
69	Hepatitis B screening immigrants	Can. Report and interview	Not enough good studies	
70	Immunization rotavirus community wide (immigrants)	Can. Report	Not enough good studies	
71	Measures to diminish contamination with campylobacter-bacteria through consumption of chicken meat to prevent gastro-enteritis	Interview [f]	Not enough good studies	
72	TBC vaccination in children from high-risk countries	Interview	Not enough good studies	
73	Rotavirus vaccination in infants	Interview		New
74	Vaccination of the prevention of human papillomavirus	Interview		New

No.		Source	Remark	Included in report
75	Promotion of taking vitamin B12 by the elderly (55+), carried out by the Netherlands Nutrition Center	Interview	Not enough good studies	
76	Promotion of taking vitamin D by the elderly (55+), carried out by the Netherlands Nutrition Center	Interview	Not enough good studies	
77	Promotion of taking vitamin D by pregnant or lactating women of ethnic minorities	Interview	Not enough good studies	
78	Computer tailored health education for the elderly	Interview	Not enough good studies	
79	Introduction of polyclinics aimed at early-diagnosis of feet infections in diabetes patients to prevent amputations	Interview	Not enough good studies	
80	Prevention of chronic kidney failure in diabetic patients	Interview	Implemented	
81	Lifestyle interventions focused on alcohol reduction of the elderly (tailoring intervention)	Interview	Not enough good studies	
82	Screening on language disorders in children	Interview	Not enough good studies	
83	Prevention of depression in high-risk teenagers	Interview	Not enough good studies	
84	Nurse led secondary prevention clinics coronary heart disease in primary care	Interview	Implemented	
85	Accompaniment to families in which parents have a mental disorder	Interview	Not enough good studies	
86	Pneumcoccal vaccination in children	Interview	Implemented	
87	Heliobacter pylori vaccination	Interview	Not enough good studies	
88	Vaccination hepatitis A in ethnic minorities	Interview	Not enough good studies	
89	BCG vaccination in ethnic minorities (TBC)	Interview	Dutch Health Council prepares advise	
90	RSV (respiratory syncytial virus) vaccination	Interview	No good and safe vaccine available	
91	Angiotensin converting enzyme (ACE) inhibitor in diabetic patients	Interview	Doubts about implementation guidelines	
92	Neonatal screening for cystic fibrosis	Interview	Will be implemented with PKU-CHT-AGS screening	
93	Biblio-therapy for adults with mild to moderate depression	Interview	Not enough good studies	
94	Prevention of burn-out	Interview	Not enough good studies	
95	Screening fragile X	Interview	Not enough good studies	
96	Physical activity programmes for diabetic patients	Interview	See: lifestyle programmes diabetic type 2 patients (no. 38)	

No.		Source	Remark	Included in report
97	Screening MCAD deficiency	Interview	Will be implemented with PKU-CHT-AGS screening	
98	Smoking cessation pregnant women	Interview	Not enough good studies	
99	Prevention of alcohol abuse pregnant women	Interview	Not enough good studies	
100	Prevention of norovirus in nursing homes through several cleaning-measures	Interview	Not enough good studies	
101	Vaccination pertussis in infants	Interview	Not enough good studies	
102	Vaccination pertussis in adolescents	Interview		New
103	Prevention of lyme disease by accurate information	Interview	Interventions not comparable	
104	Vaccination lyme disease	Interview	No vaccine at the European market	
105	Screening albuminuria in general population to prevent CHD/kidney disease	Interview	Not enough good studies	

[a] Interventions that are described in the report: “De kosteneffectiviteit van preventie: een verkennende studie” by Dirkmaat T, Genugten MLL van, Wit GA de (2003).
[b] Update not necessary because intervention is part of the recent report “Economische evaluatie van preventie; Kansen voor het Nederlandse volksgezondheidbeleid” by Vijgen SMC, Busch MCM, Wit GA de, Zoest F van, Schuit AJ.
[c] Interventions that are included in the report: “Economische evaluatie van preventie; Kansen voor het Nederlandse volksgezondheidbeleid” by Vijgen SMC, Busch MCM, Wit GA de, Zoest F van, Schuit AJ. It are interventions for which enough good studies were found.
[d] Interventions that are not included in the report: “Economische evaluatie van preventie; Kansen voor het Nederlandse volksgezondheidbeleid” by Vijgen SMC, Busch MCM, Wit GA de, Zoest F van, Schuit AJ. It are interventions for which not enough good studies were found.
[e] Interventions found in the report “Economic evaluation across the four faces of prevention: a Canadian perspective” by Goldsmith LJ, Hutchison B, Hurley J (2004).
[f] Inventory of interventions based on interviews.

Appendix 3: Questions regarding implementation and translation of foreign study results to the Dutch context

9. What is your expertise?

10. Did we include all important economic evaluation studies in our overview of the topic you have knowledge on?

11. Are there currently Dutch studies being carried out on the cost-effectiveness of this preventive intervention?

12. Do you know of any studies on the intervention that are not published because of lack of (cost-)effectiveness?

13. Is there sufficient evidence for the effectiveness of the preventive intervention?

14. To what extent are results from foreign studies about the cost-effectiveness transferable to the Dutch setting / On which issues does the context of foreign studies differ most from the Dutch situation? Think of:
    - demographic factors,
    - epidemiological factors,
    - cultural factors,
    - differences between countries in medical procedures,
    - differences between countries in health care consumption,
    - differences between countries in financing of health care,
    - differences between countries in financial incentives to health care suppliers and patients,
    - absolute and relative price differences between countries.

15. To what extent is the intervention already implemented in the Netherlands?

16. Which bottlenecks exist regarding implementation of the intervention?

17. Which factors encourage implementation?

18. Several countries have implemented the intervention. Why is it implemented there and not in the Netherlands?

19. Is the intervention feasible:
    - practically,
    - financially,
    - ethically?

20. How should the intervention be implemented in the Netherlands?

21. Which initiatives are already set up around the implementation of the intervention? Think of:

- ZonMw funding,
- experimental projects,
- advisory bodies,
- consensus meetings et cetera

22. Does everyone have the same opinion on implementation of the intervention or are there major differences in opinions?

23. Which other experts (either with a practical view or with a more theoretical vision**)** could I approach for an interview about this intervention?

24. Are you willing to comment on our draft text about this intervention?

25. May I include your name in the list of experts that is to appear in our report?

Appendix 4: Keywords used for the literature search

Basic keywords:
(Costs and cost analysis) in mesh

Intervention	**Keywords**
Screening for group B streptococcal infections	- streptococcus agalactiae - streptococcal-infections - GBS - prevention in mesh
vaccination against hepatitis B	- hepatitis b - HBV - vaccine/vaccination - immunization/immunization - risk groups
Rotavirus vaccination	- rotavirus - vaccine/vaccination - immunization/immunization
Pertussis vaccination of adolescents	- pertussis - vaccine/vaccination - immunization/immunization - adolescents
Human papillomavirus vaccination	- HPV - vaccine/vaccination - immunization/immunization
Fluoridation of drinking water for the prevention of dental decay	- fluoridation - dental decay - prevention in mesh
Mandatory folic acid fortification of staple foods to prevent neural tube defects	- folic acid - fortification - neural tube defects - prevention in mesh
Vaccination against varicella zoster virus	- varicella - vaccine/vaccination - immunization/immunization
Stop smoking interventions	- smoking cessation - GP counseling - Prevention in mesh
Vaccination of working adults against influenza	- Influenza - working population - working adults - adults - vaccine/vaccination - immunization/immunization
Pneumococcal vaccination of elderly people	- pneumococcal/pneumococcus - elderly - vaccine/vaccination - immunization/immunization

Appendix 5: Experts interviewed to identify preventive interventions

Experts interviewed to identify preventive interventions

M. Van den Akker-Van Marle (TNO)
C. Baan (PZO, RIVM)
W. Bemelmans (PZO, RIVM)
Y. van Duynhoven (CIB, RIVM)
A. Havelaar (MGB, RIVM)
N. de Jong (CVG, RIVM)
M. van de Laar (CIB, RIVM)
F. van der Lucht (VTV, RIVM)
A. Lugner (CIB, RIVM)
M-J. Mangen (PZO, RIVM)
W-J. Meerdink (ErasmusMC)
S. Picavet (PZO, RIVM)
J. Polder (VTV, RIVM)
C. van Rossum (CVG, RIVM)
M. Postma (RUG)
C. Schoemaker (VTV, RIVM)
L. Veerman (Erasmus MC)
R. Welte (GSK, Germany)
K. Witte (VTV, RIVM)

Experts interviewed on feasibility and implementation

M. van den Akker- Van Marle (TNO)
H. Boot (CIB, RIVM)
I.A. Brouwer (VU)
J.M. ten Cate (VU, Acta)
M.C. Cornel (VU MC)
T. Feenstra (PZO, RIVM)
S. de Greeff (CIB, RIVM)
S. Hahné (CIB, RIVM)
J. Kloosterman (CVG, RIVM)
M-J. Mangen (PZO, RIVM)
H. De Melker (CIB, RIVM)
S. Mylius (CIB, RIVM)
F. Mooi (CIB, RIVM)
M. van der Sande (CIB, RIVM)
MAJM Trijbels-Smeulders (Flevoziekenhuis)
F.J.J. Verhagen (CVG, RIVM)
J.F.M. Versteegh (MEV, RIVM)
HIJ. Wildschut (Erasmus MC)

Appendix 6: Background tables for the preventive interventions in chapter 3

Table 6.1: Screening for group B streptococcal infections

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
Akker-Van Marle, 2005	The Netherlands	1) Risk based strategy 2) Screening based strategy, 35-37 wk 3) Combi strategy, 35-37 wk 4) Current Dutch Guideline	No treatment	1) €7600 per QALY 2) €59,300 per QALY 3) €9100 per QALY 4) €48,800 per QALY	Price year unknown	- Design: decision analysis - Perspective: societal - Effectiveness: depends on screening strategy: 186-766 QALYs - Costs: depend on screening strategy: €5-45M (price year: NS) - Discounting: 3% (costs and benefits) - Sensitivity: mortality rate, long term sequelae, long term costs - Remark: Introducing the polymerase chain reaction (PCR) test may lead to a more favourable cost-effectiveness ration (for intervention 2 and 3) €2300 per QALY gained for the combined screening/risk-based strategy
Stan, 2001	Switzerland	1) Risk-based strategy 2) Screening strategy, 35-37 wk	Current policy	1) £60,700 per averted sepsis case 2) £473,600 per averted sepsis case	1) €101,100 2) €789,000	- Design: decision analysis - Perspective: societal - Effectiveness: strategy 1: 67 averted cases; strategy 2: 102 averted cases - Costs: strategy 1: 7.5 M£; strategy 2: 23.2 M£ (price year: 1999) - Sensitivity: prevalence of maternal colonization, sensitivity of antenatal GBS culture
Mohle-Boetani, 1999	US	1) Risk based strategy 2) Risk-based strategy, 48 hrs observation	Usual obstetric practice (no IPA)	1) Net savings of $1,1 million 2) $130,000 per LYS	1) Net savings of €1,2M 2) €139,800 per LYS	- Design: decision analysis - Perspective: medical - Effectiveness: 66 averted cases in both strategies - Costs: strategy 1: $1.7 M; strategy 2: $10.9 M (price year: 1997)

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
						- Discounting: 3% (costs and benefits) - Sensitivity: costs of antibiotics
Bentitz, 1999	US	1) Screening-based strategy, 28 wk 2) Risk-based strategy 3) Screening based strategy, 35-37 wk 4) Combi-strategy, 35-37 wk 5) Universal IAP	No intervention	1) $22,215 per case prevented 2) $3067 per case prevented 3) $11,925 per case prevented 4) $9720 per case prevented 5) $12,049 per case prevented	Price year unknown	- Design: decision analysis - Perspective: medical - Effectiveness: 33-80% of the GBS cases averted - Costs: only direct costs were included (price year: not reported) (not discounted (short time frame)) - Sensitivity: results were not sensitive to any of the parameters included in the sensitivity analysis
Garland, 1995	Australia	1) Screening based strategy, 28 wk 2) Combi strategy 28 wk9 3) Risk-based strategy	No intervention	1) $6663 per case prevented 2) $7416 per case prevented 3) $270 per case prevented	1) €5700 2) €6400 3) €230 Price year 1993 is assumed	- Design: decision analysis - Perspective: medical - Effectiveness: resp. 46, 38, 80 cases prevented - Costs: resp. 7.9, 8.6, 2.3 MAus$ (price year: 1993/1994) (not discounted) - Sensitivity: compliance of screening
Yancey, 1994	US	1) Screening-based strategy, 28 wk 2) Combi-strategy, 26-28 wk	No screening, no treatment with prophylaxis	1) $11,900 per case averted 2) $22,900 per case averted	Price year unknown	- Design: decision analysis - Perspective: not reported - Effectiveness: attack rate 1.08 and 1.64 - Costs: 30000 and 22000 $ (no discounting price year? - Sensitivity: no sensitivity analysis
Mohle-Boetani, 1993	US	1) Risk based strategy 2) Screening- based strategy, 28 wk7	No intervention	1) $28,800 per case prevented 2) $12,900 per case prevented	Price year unknown	- Design: decision analysis - Perspective: societal - Effectiveness: 3300 and 3200 cases averted - Costs: $95 and 41.3M (price year not reported) - Discounting: 5% (costs) - Sensitivity: not sensitive

Table 6.2: Universal hepatitis B vaccination

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
De Wit, 2000	The Netherlands	Universal vaccination of infants	Prenatal screening	Costs per LYG (Dutch guilders) 56,155 (high variant) 126,845 (medium variant) 164,549 (low variant)	 €29,200 €66,000 €85,600	- Design: an epidemiologic model and a decision analytic model - Perspective: healthcare - Effectiveness: (efficacy: 90%) number of prevented infections and life years saved; high variant: 36,404; 6,153, medium variant: 17,678; 2,836, low variant: 13,991; 2,203 - Costs: (price year: 2000) - Discounting: 4% (costs and benefits) - Sensitive to: vaccine costs, prevalence and incidence, discount rate health gains - Remarks: the three variants differ in HBV prevalence among immigrants: high variant: 6%, medium variant: 1,7% and low variant: 1%
Zurn, 2000	Switzerland	1) Prenatal screening 2) Universal vaccination of infants 3) Universal vaccination of school children 4) Universal vaccination of infants and school children (during a period of 12 years) 5) Universal vaccination of infants, school children (during a period of 12 years) and adolescents	Vaccination of high-risk groups	Costs per LYS (Swiss Francs) 1) 59,300 2) 59,290 3) 53,970 4) 52,400 5) 60,960	1) €86,600 2) €32,200 3) €29,300 4) €28,500 5) €33,200	- Design: a lifetime decision analytic model - Perspective: society - Effectiveness: 1) 137; 2) 871; 3) 823; 4) 1557; 5) 2202 years of life saved - Costs intervention: 1) 3 302,310; 2) 9 947,740; 3) 13 170,600; 4) 19 869,250; 5) 29 207,150 (price year: 1996) - Discounting: 3% (costs and benefits) - Sensitive to: prevalence, vaccine price and discount rate

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
		(during a period of 3 years)				
Wiebe, 1997	Canada	1) Universal vaccination of infants 2) Universal vaccination of 10-years olds 3) Universal vaccination of 12-years olds	Prenatal screening	Costs per LYS (Canadian dollars) 1) 15,900 2) 97,600 3) 184,800	1) €14,900 2) €91,300 3) €172,800	- Design: a lifetime Markov decision analytic model - Perspective: healthcare system - Effectiveness: not reported - Costs: not reported (price year: 1993) - Discounting: 5% (costs and benefits) - Sensitive to: discount rate, incidence, immunization costs, the rate at which vaccine protection was lost - Remarks: indirect costs and effects, such as increased productivity and less pain and suffering were not considered
Garuz, 1997	Spain	1) Universal vaccination of infants 2) Universal vaccination of adolescents (12/13-years olds) 3) Universal vaccination of infants and adolescents (for a period of 12 years) 4) Combination of the most cost-effective programme and prenatal screening	Vaccination of risk groups	Costs per case prevented with undiscounted respectivily discounted benefits (US dollars) 1) 1875; 2564 2) 603; 850 3) 834; 1170 4) 590; 820	1) €2200-2900 2) €690-980 3) €960-1300 4) €680-940	- Design: a Markov decision analytic model - Perspective: society - Effectiveness: number of cases prevented after respectivily 10, 20 and 30 years 1) 3,569, 13,648, 43,733 2) 16,055, 66,024, 99,308 3) 19,622, 79,672, 143,041, 16,665 - Costs: not reported (price year: 1993) - Discounting: 5% (costs and benefits) - Sensitive to: vaccine price
Fenn, 1996	UK	1) Universal vaccination of infants 2) Universal vaccination of children (6-years	No vaccination	Costs per LYG with undiscounted respectively discounted benefits (UK pounds) 1) 5234; 227,130	1) €10,000; 435,000	- Design: a Markov decision analytic model - Perspective: healthcare - Effectiveness: not reported - Costs: not reported (price year: 1992/93) - Discounting: 6% (costs and benefits) - Sensitive to: incidence and reporting rate of

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
		olds) 3) Universal vaccination of adolescents (11-years olds) 4) Universal vaccination of infants and adolescents		2) 9646; 301,365 3) 8470; 233,379 4) 6827; 231,115	2) €18,500; 577,200 3) €16,200; 447,000 4) €13,100; 442,700	infections, transition probabilities in the chronic stage of the disease
Antonanzas, 1995	Spain	1) Universal vaccination of infants 2) Universal vaccination of adolescents (12-years olds) 3) Universal vaccination of infants and adolescents (for a period of 12 years)	No vaccination	Costs per case prevented with undiscounted respectively discounted benefits (Spanish Pesetas) after 10 years: 1) 158,000; 254,000 2) 49,000; 82,000 3) 79,000; 129,000 after 20 years: 1) 34,000; 81,000 2) 2000; 4000 3) 11,000; 24,000	1) 1200; 2000 2) 380; 640 3) 620; 1010 1) 270; 640 2) 15;30 3) 90;190	- Design: a compartmental and a Markov decision analytic model - Perspective: healthcare - Effectiveness: avoided cases of HBV infections 1) 5,493 (after 10 years), 13,644 (after 20 years) 2) 15,100 (after 10 years), 33,500 (after 20 years) 3) 20,007 (after 10 years), 68,100 (after 20 years) - Costs: not reported (price year: 1992) - Discounting: 5% (costs and benefits) - Sensitive to: cost of vaccine, discount rate and chronic infection healthcare costs
Mangtani, 1995	UK	1) Universal vaccination of infants 2) Universal vaccination of pre-adolescents	Vaccination of high-risk groups	Costs per LYG with undiscounted respectively discounted benefits (pounds) 1) 2568; 94,821 2) 2824; 51,817	Costs per LYG with undiscounted respectively discounted benefits (2005 euros) 1) €5,600; 206,600 2) €6200; 112,900	- Design: decision analytic model - Perspective: healthcare - Effectiveness: undiscounted respectively discounted years gained 1) 6 381; 173 2) 5 549; 302 - Costs: (price year: 1990) 1) 16 386 431 2) 15 668 482 - Discounting: 6% (costs and benefits) - Sensitive to: discount rate of health gains, cost of vaccine, relative risk s of mortality with HBV, prevalence of HBV

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
						- Remarks: the costs per LYG of vaccination of high-risk groups was 8,564; 124,779. Additional cost per LYG 1) 1,537; 77,085 and 2) 1,658; 32,125

Table 6.3: Rotavirus vaccination of newborns

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
Carlin et al., 1999	Australia	Vaccination programme with tetravalent rhesus rotavirus vaccine (RRV-TV)	No vaccination strategy	Vaccination programme is cost-neutral at vaccine price of US$19 per dose (healthcare system) and US$26 (societal)	Vaccination programme is cost-neutral at vaccine price of €20 per dose (healthcare system) and €28 (societal)	- Design: decision analysis - Vaccination costs: $30 (price year: 1998) - Vaccine efficacy: 70% against severe disease; 85% against hospitalizations - No discounting due to short time frame - Perspective: healthcare system, societal - Sensitive to: vaccine price and whether separate immunization visits would be required.
Takala et al., 1998	Finland	Vaccination with tetravalent rhesus rotavirus vaccine (RRV-TV)	No vaccination strategy (placebo)	Break-even cost of vaccination per infant is US$15.46 (excluding the cost of the vaccine)	Break-even cost of vaccination per infant is €18 (excluding the cost of the vaccine)	- Design: randomized, double-blind, placebo-controlled trial - Vaccination costs: NS (price year: 1993) - Vaccine efficacy: 95% against severe RV in the first season and 90% in the second - No discounting due to short time frame - Perspective: societal - Sensitive to: cost of hospitalization, vaccine costs
Tucker et al., 1998	US	Vaccination programme with tetravalent rhesus rotavirus vaccine (RRV-TV). 3 doses in the first 6 months	No vaccination strategy	Break-even price per dose is US$9 (healthcare system) and US$5 (societal)	Break-even price per dose is €10 (healthcare system) and €5 (societal)	- Design: decision analysis - Vaccination costs: $20 (price year: 1996) - Vaccine efficacy: 50% against RV diarrhea, 85% against hospitalizations and deaths - Discounting: 3% per annum for costs and benefits - Perspective: healthcare system, societal - Sensitive to: vaccine price, vaccine efficacy, and hospitalizations
Griffiths et al., 1995	US	1) Vaccination with tetravalent rhesus rotavirus vaccine (RRV-TV) 2) Vaccination with serotype 1 rhesus	No vaccination strategy (placebo)	Break-even costs of vaccination per infant are (excluding the cost of the vaccine): 1) US$11 (RRV-TV) 2) US$12 (S1V)	Break-even costs of vaccination per infant are (excluding the cost of the vaccine): 1) €13 (RRV-TV)	- Design: randomized, double-blind, placebo-controlled trial - Vaccination costs: NS (price year: 1992) - Vaccine efficacy: NS - No discounting due to short time frame - Perspective: societal

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
		vaccine (S1V)			2) €14 (S1V)	- Sensitive to: vaccine costs
Smith et al., 1995	US	National immunizations of children under 1 year with rotavirus vaccine	No vaccination strategy	Saving of $78 per case prevented (healthcare system) and saving of $459 per case prevented (societal)	Saving of €90 per case prevented (healthcare system) and saving of €528 per case prevented (societal)	- Design: decision analysis - Vaccination costs: $20 (price year: 1993) - Vaccine efficacy: 50% against RV - Discounting: 4% per annum for costs and outcomes (2-8%) - Perspective: healthcare system, societal - Sensitive to: vaccine price and vaccine efficacy

Table 6.4: Pertussis vaccination of adolescents

First author, publication year	Country	Intervention scenario	Reference scenario	Original results economic evaluation	Converted result (2005 Euros)	Characteristics economic evaluation
Caro, 2005	US and Canada	Adding an adolescent acellular booster dose (between the ages of 11 and 18 years) to the current US pertussis immunization schedule (as a combined dTaP)	The current US immunization practice of vaccinating with a combined diphtheria-tetanus (dT) vaccine (DTaP or DTaP-IPV at 2,4,6,18 months and at 4-6 years)	Base case: 20% herd immunity $22,023/LYG (health care) $6,253/LYG (societal) Cost-saving (35% herd immunity) $187,081/LYG (5% herd immunity)	€21,900 (health care) €6,200 (societal) €185,900	- Design: decision analysis - Perspective: health care and societal - Effectiveness: initial vaccine efficacy was 85%, the coverage rate was 80% - Costs: 2002 US dollars, direct and indirect costs, no costs of vaccine administration - Discounting: 3% (costs and benefits) - Sensitivity: the duration of effectiveness of immunization - Remarks: lifetime horizon
Lee, 2005	US	1) 1-time adolescents vaccination at 11 years of age 2) 1-time adult vaccination at 20 years of age 3) Adult vaccination with 10-year boosters 4) Adolescent and adult Vaccination with 10-year boosters 5) Postpartum vaccination	No vaccination (or status quo, with children being vaccinated at 2, 4, 6 and 12-15 months and 4-6 years of age)	1) $23,000/QALY (HCP), $20,000/QALY (societal) 2-5) dominated, more costly and less effective	€22,400 (HCP) \€19,500 (societal)	- Design: decision-analysis (Markov-model) - Perspective: health care payer and societal - Effectiveness: reduction in infant disease varies from 10-40% - Costs: 2004 US dollars, direct and indirect costs - Discounting: 3% (costs and benefits) - Sensitivity: disease incidence, vaccine efficacy, frequency of vaccine adverse events, and vaccine costs. - Remarks: lifetime horizon and adolescent or adult vaccination strategies were assumed to have no impact on transmission to infants in the baseline analysis.
Iskedjian, 2004	Ontario, Canada	Combined vaccination programme (CVP)	Current practice (CP)	MOH: $can 168 per pertussis case avoided	MOH: €140 per pertussis case	- Design: decision analysis (dynamic model) - Perspective: Ontario Ministry of Health,

First author, publication year	Country	Intervention scenario	Reference scenario	Original results economic evaluation	Converted result (2005 Euros)	Characteristics economic evaluation
		including a diphtheria, accelular pertussis and tetanus (dTacp) vaccine at 12 years of age		3% discounting: $can 188/pca Societal: cost-saving	avoided 3% discounting: €160/pca Societal: cost-saving	Welfare and Sports(MoH) and societal - Effectiveness: vaccine efficacy 85% - Costs: 2001 CAN$, direct and indirect costs - Discounting: 3% (costs and benefits) - Sensitivity:
Purdy, 2004	US	1) Universal immunization all persons >= 10 y of age 2) Immunization all adolescents 10-19 y of age	No immunization	Break-even cost per vaccination: 1) $31.68 2) $36.92	1) €31.00 2) €37.00	- Design: decision analysis - Perspective: societal - Effectiveness: 10 year protection, vaccines provide 88% protective efficacy, 40% vaccine compliance, 40% parent-to infant transmission rate - Costs: 2002 US dollars, direct and indirect costs - Discounting: 3% - Sensitivity: - Remarks: study outcome is the amount of money that exactly balances societal disease burden costs that are preventable by vaccination against vaccine-associated costs.
Edmunds, 2002	England and Wales	1) An acellular pertussis booster doses at 4 years of age 2) An acellular pertussis booster doses at 15 years of age	No vaccination	HCP: 1) 13,345 pounds/LYG (60% of cases prevented in younger children) - 8463 pounds/LYG (80%) 2) 13,019 pounds/LYG (60%) - 7661 pounds/LYG (80%) Societal: 1) 6586 pounds/LYG (60% of cases prevented in younger children) -	HCP: 1) €22,200 (60%) - €14,100 (80%) 2) €21,700 (60%) - €12,800 (80%) Societal: 1) €11,000 (60%) - €4,100 (80%)	- Design: decision analysis (dynamic transmission model) - Perspective: health care provider (HCP) and societal - Effectiveness: vaccine efficacy 95% and coverage booster 84 - Costs: 1999/2000 Pounds, direct and indirect costs - Discounting: 3% (costs and benefits) - Sensitivity: degree of herd immunity protection, mortality rate, degree of underreporting, vaccine cost, discount rate for both the costs and benefits.

First author, publication year	Country	Intervention scenario	Reference scenario	Original results economic evaluation	Converted result (2005 Euros)	Characteristics economic evaluation
				2489 pounds/LYG (80%) 2) 4645 pounds/LYG (60%) - -633 pounds/LYG (80%)	2) €7700 (60%) - € -1100 (80%) Assumed price year 1999	

Table 6.5: Human papillomavirus vaccination of adolescents

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 Euros)	Characteristics economic evaluation
Taira, 2004	US	1) A HPV-16 and 18 vaccine was given to girls at age 12 (in three doses) and a booster at 22 years 2) HPV-16 and 18 vaccination of both girls and boys at age 12 and a booster at 22 years	1) No vaccination strategy 2) A HPV-16 and 18 vaccine was given to girls at age 12 (in three doses) and a booster at 22 years	1) $14,583 per QALY gained 2) $442,039 per QALY gained	Price year unknown	- Design: hybrid model by combining the cohort model used by Sanders et al., with a transmission model, thus herd immunity effects were included - Perspective: not reported - Effectiveness: duration protection is 10 years, vaccine efficacy 90% and coverage is 70% - Costs: vaccine is $300 (initial) and $100 (booster) – - Price year: not known - Discounting: yes, but no % mentioned - Sensitivity: only vaccinating men and boys was sentitive to changes in key variables
Goldie, 2004	US	Here, out of the 14 strategies evaluated, only the cost-effective strategies are shown: 1) Vaccination (90% efficacy) and current screening practice 2) Screening (HPV test incl.) starting at age 30 every 5 years and vaccination (90% efficacy) at 12 years 3) Screening (HPV test incl.) starting at age 35 every 5 years and	1) Current US screening practice 2) Idem except starting age screening is 25 years 3) Screening (HPV test incl.) starting at age 30 every 5	Here, out of the 14 strategies evaluated, only the cost-effective strategies are shown: 1) US$ 24,300/QALY 2) US$ 17,200/QALY 3) US$ 12,300/QALY 4) US$ 22,200/QALY	1) €24,200 2) €17,100 3) €12,200 4) €22,100	- Design: decision analysis (Markov model) - Perspective: societal , but no indirect costs were included (health care perspective) - Effectiveness: 100% coverage, 90% vaccine efficacy, lifetime duration of protection - Costs: 2002 US dollars, direct costs - Discounting: 3% (costs and effects) - Sensitivity: duration of vaccine efficacy, frequency of screening, starting age of screening. - Remarks: lifetime horizon

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 Euros)	Characteristics economic evaluation
		vaccination (100% efficacy) at 12 years 4) Screening (HPV test incl.) starting at age 30 every 5 years and vaccination (80% efficacy) at 12 years	years 4) Screening (HPV test incl.) starting at age 21 every 5 years			
Kulasingam, 2003	US	40 strategies were examined comparing screening only conducted every 1,2,3, and 5 years with a strategy of screening plus vaccination at identical intervals , varying the ages of screening onset (age 18 years, 22 years, 24 years, 26 years, and 30 years)		The screening only interventions with less frequent intervals and later starting ages are cost-effective. Combination with vaccination are not		- Design: decision analysis (Markov model) - Perspective: health care - Effectiveness: 100% coverage, 90% vaccine efficacy, duration of protection is 10 years - Costs: US$ 2001, direct medical costs - Discounting: 3% (costs and effects) - Sensitivity: the vaccination starting age, the HPV types covered, vaccine efficacy, duration of protection
Sanders, 2003	US	1) School-based HPV vaccination of females aged 12 years + standard care 2) Sensitivity analysis: a. Lifetime immunity b. Utility of high-grade SIL c. Higher incidence HPV d. Screening every 5 years	Standard care (conventional, biennial Papanicoleau test screening starting at age 16 years)	1) 22,755/QALY 2) Sensitivity analysis: a. $12,682 b. $16,927 c. $12,664 d. $7238	1) €22,800 2) Sensitivity analysis: a. €12,700 b. €17,000 c. €12,700 d. €7300	- Design: decision analysis - Perspective: third-party payer - Effectiveness: 70% coverage, 75% vaccine efficacy, duration of protection is 10 years, but booster shots every 10 years are required - Costs: 2001 US$, no indirect costs - Discounting: 3% (costs and effects) - Sensitivity: vaccine efficacy

Appendix 7: Background tables for the preventive interventions in chapter 4

Table 7.1: Fluoridation of drinking water

First author, publication year	Country	Intervention scenario	Reference scenario	Original result of economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
O'Connell, 2005	US	Community water fluoridation programme	No fluoridation programme	Cost-saving (BCR: 22-135$)	Cost-saving (BCR: €22-133)	- Design: modelling - Perspective: societal - Effectiveness: 25% reduction of annual decay increment - Costs: USD 2003 - Discounting: 3% (costs) - net savings: programme costs (one time fixed costs and annual operating costs) minus averted decay treatment costs - Sensitivity analysis: fluoridation effectiveness, and decay increment estimate
Griffin, 2001	US	Community water fluoridation	No water fluoridation	Cost-saving	NA	- Design: calculation - Perspective: societal - Effect size: 25% reduction of annual decay increment - Costs: USD 1995 - Discounting: 4% (costs) - Net savings: programme costs minus averted decay treatment costs - Sensitivity analysis: cost of caries, decrease in decay increment, community size
Wright, 2001	New Zealand	Water fluoridation	No water fluoridation	Cost-saving	NA	- Design: calculation - Discount rate: 5% (costs and benefits) - Effect size: 0.33 averted decayed surfaces - Costs: NZ$, 1999 - Net savings: programme costs minus averted decay treatment costs - Perspective: societal - Sensitivity analysis: community size

First author, publication year	Country	Intervention scenario	Reference scenario	Original result of economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
Birch, 1990	UK	Water fluoridation	No water fluoridation	Cost-effectiveness varies between £1.6 per DMFT person years reduced (large community, high caries incidence), and £19.46 per DMFT person years reduced (small communities, low caries incidence)	Price year unknown	- Design: calculation - Perspective: societal - Effectiveness: circa 16,000 and 65,000 reduced DMFT person years - Discount rate: 5% (costs) - Cost-effectiveness: fluoridation costs per DMFT person years reduced by fluoridation - Sensitivity analysis: community size, caries incidence

Table 7.2: Mandatory folic acid fortification of staple foods

First author, publication year	Country	Intervention scenario	Reference scenario	Original result of economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
Grosse, 2005	US	Folic acid fortification of cereal grain (140 µg. per 100 g. grain)	No fortification	Cost-saving ($88,000000-$145,000000)	Cost-saving (€87,500000-€144,100000)	- Design: decision analysis - Perspective: societal - Effectiveness: 612 averted cases of NTD - Costs: intervention costs: 3 M$, total benefit due to prevention of NTD: 425 M$ (price year 2002) - Discounting: 3% (costs) - Sensitivity analysis: still cost-saving in worst case scenario
Kelly, 1996	US	1) Folic acid fortification of cereal grain with 140 µg. folic acid per 100 g grain 2) Folic acid fortification of cereal grain with 350 µg. folic acid per 100 g grain 3) Folic acid fortification of cereal grain with 700 µg. folic acid per 100 g grain 4) Promoting voluntary use of folic acid supplements	1) No fortification 2) idem 3) idem 4) idem	1) Cost-saving, but dominated by 2 and 3 2) Cost-saving, but dominated by 3 3) Cost-saving: -$13,000/QALY 4) Dominated by 1, 2, 3	1) NA 2) NA 3) -€15,000 4) NA	- Design: decision analysis - Perspective: societal - Effectiveness: 50% risk reduction for NTD - Costs: (price year 1993) Discount rate: 5%(Costs) - Sensitivity analysis: ? - Remark: No dose-response relation, but all-or-nothing effect
Romano, 1995	US	1) Low-level folic acid fortification of cereal grain with (140 µg. folic acid per 100 g grain)	1) No fortification (33% already receive	1) Cost-saving (benefits to costs ratio: 4) $92,000 per case averted 2) Cost-saving	1) €113,000 2) €80,000 3) €162,200	- Design: decision analysis - Perspective: societal - Effectiveness: 50% of NTD cases prevented - Costs: strategy 1: 27.9 M$, strategy 2:: 49.2 M$ (price year 1991)

First author, publication year	Country	Intervention scenario	Reference scenario	Original result of economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
		2) High-level folic acid fortification of cereal grain with (350 µg. folic acid per 100 g grain) 3) Promoting voluntary use of folic acid supplements (400 µg. of folic acid)	enough folic acid from supplements or diet) 2) idem 3) idem	(benefits to costs ratio: 6) $65,000 per case averted 3) $132,000 per case averted		- Discount rate: 4%(Costs) - Sensitivity analysis

Table 7.3: Vaccination against varicella zoster virus

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
Coudeville, 2005	Germany/France	1) Universal vaccination of toddlers 2) Universal vaccination of toddlers + catch-up for 2-11 year-olds during the first year	1) No vaccination 2) Universal vaccination of toddlers	1) Cost-saving from both societal and health system perspective in both Germany and France 2) Cost-saving from societal perspective in both countries	NA	- Design: Modelling study (epidemiological dynamic model) - Perspective: societal and health system - Vaccine efficacy: 97% - Discount rate: 3% - Sensitivity analysis: - Remark: Coverage rate is key element of level of benefit gained from vaccination
Coudeville, 2004	Italy	1) Universal vaccination of toddlers 2) Universal vaccination of toddlers + catch-up for 6-year-olds during first 5 years 3) Universal vaccination of toddlers + catch-up for 2-11 year-olds during the first year	1) No vaccination 2) Universal vaccination of toddlers 3) Universal vaccination of toddlers	1) Cost-saving from both societal and health system perspective 2) Cost-saving from societal perspective 3) Cost-saving from societal perspective	NA	- Design: Modelling study (epidemiological dynamic model) - Vaccine efficacy: 97% - Discount rate: 3% - Perspective: societal and health system - Sensitivity analysis:
Ginsberg, 2004	Israel	Universal vaccination of 12 months old children	No vaccination	Cost-saving from both perspectives (BCR: 19.3:1, and 1.6:1)	NA	- Design: modelling - Vaccine efficacy: 88% - Discount rate: 3% - Perspective: society, and healthcare - Sensitivity analysis: vaccine costs, and work losses
Banz, 2003	Germany	1) Universal vaccination of 15 months old children 2) Universal vaccination of 15	1) No vaccination 2) No vaccination	Cost-saving from both perspectives: BCR: 4.1:1 (2.3-6.3) and 1.8:1	NA	- Design: decision analytic model - Vaccine efficacy: 86% - Discount rate: 5% - Perspective: societal, and third-party payer - Sensitivity analysis: vaccine coverage,

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
		months old children + catch-up of adolescents				discount rate, costs of work loss, vaccine price, hospitalization costs - Remark: Payer perspective also cost-saving because third-party payers reimburse large part of lost earning of parent
Brisson, 2003	England/Wales	1) Universal vaccination of infants 2) Universal vaccination of infants + catch-up for 2-11 year-olds during the first year	1) No vaccination 2) No vaccination	1) QALY loss 2) QALY loss	NA	- Design: dynamic modelling study - Vaccine efficacy: 100% - Discount rate: 3% - Perspective: health provider (only direct medical costs) - Sensitivity analysis: vaccine efficacy, zoster immunity duration; discount rate, time frame - Remark: This model assumed increase of zoster as a result of infant vaccination
Hsu, 2003	Taiwan	Universal vaccination of 15 months old children	No vaccination	Cost-saving from societal perspective: (BCR: 2.1:1), but not from health system perspective (BCR: 0.3:1)	NA	- Design: Markov decision model - Vaccine efficacy: 95% - Discount rate: 4% - Perspective: societal, and payer' - Sensitivity analysis: vaccine price

Table 7.4: Stop smoking interventions

First author, year of publication	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted results (2005 Euros)	Characteristics economic evaluation
Cornuz, 2006	Canada, France, Spain, UK, US, Switzerland	1) GP counselling + Nicotine gum per country 2) GP counselling + Nicotine patch per country 3) GP counselling + Nicotine spray per country 4) GP counselling + nicotine inhaler per country 5) BU per country	GP counselling	1) $2230/LYG for men in Spain- $7643/LYG for women in the US 2) $1758/LYG for men in Spain to $5131/LYG for women in the UK 3) $1935/LYG for men in Spain to $7969 for women in the US 4) $3480/LYG for men in Switzerland to $8700/LYG for women in France 5) $792/LYG for men in Canada to $2922 for women in the US	1) €2,197/LYS for men in Spain- €7,531/LYS for women in the US 2) €1,732/LYS for men in Spain to €5,056/LYS for women in the UK 3) €1,907/LYS for men in Spain to €7,852 for women in the US 4) €3,429/LYS for men in Switzerland to €8,572/LYS for women in France 5) €780/LYS for men in Canada to €2,879 for women in the US Assumed price y2003	- Design: decision analysis (Markov-chain cohort model) - Perspective: third-party-payer - Effectiveness: OR counselling: 1.73, OR nicotine replacement therapy: 1.66 (gum), 1.80 (patch), 2.35 (spray), 2.14 (inhaler) (discount rate: 3%) - Costs: US$ (price year: 2002/2003) (discount rate: 3%) - Sensitive to: discount rate, treatment efficacy and natural quit rate
Feenstra, 2005	NL	1) Minimal counselling 2) GP counselling 3) GP counselling + nicotine replacement therapy (NRT): patches or gum.	Current practice in the Netherlands	1) € 9100 per QALY 2) € 8800 per QALY 3) € 13,400 per QALY	1) €9200 per QALY 2) €8900 per QALY 3) €13,600 per QALY	- Design: decision analysis - Perspective: health care - Effectiveness: cessation rate GP counselling (H-Mis): 8%, H-Mis + NRT: 14% (discount rate: 4%) - Costs: GP counselling (H-Mis): €26 per smoker, H-Mis + NRT: 183 (price year: 2004) (discount rate: 4%) - Sensitive to: discount rates and time horizon.
Cornuz, 2003	Switzerland	1) GP counselling +	GP	1) Costs per LYG	1) Costs per LYG	- Design: decision analysis

First author, year of publication	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted results (2005 Euros)	Characteristics economic evaluation
		nicotine replacement therapy (NRT): gum, patch, spray and inhaler 2) GP counselling + bupropion sustained release (BSR)	counselling	(depends on age and gender): € 3113-8799 (gum and patch) 2) Costs per LYG (depends on age and gender): € 1,768-3,646 LYS.	(depends on age and gender): € 3500-9800 (gum and patch). 2) Costs per LYG (depends on age and gender): € 2000- 4100 LYS.	- Perspective: third-party-payer - Effectiveness: OR counselling: 1.73, OR nicotine replacement therapy: 1.63 (gum), 1.73 (patch) (discount rate: 3%) - Costs: ns (price year: 2000) (discount rate: 3%) - Sensitive to: discount rate and natural quit rate
Song, 2002	UK	1) GP counselling + nicotine replacement therapy (NRT) 2) GP counselling + bupropion sustained release (BSR)	Standard care: brief advice or counselling	1) $1441 per QALY 2) $920 per QALY	1) €1400 per QALY 2) €900 per QALY	- Design: decision analysis - Perspective: health care - Effectiveness: quit rate counselling: 10%, OR was 1.67 with NRT versus placebo (discount rate: unclear) - Costs: US$148.44 (price year: 2001) (no discounting because of short term costs) - Sensitive to: effects and costs
Stapleton, 1999	UK	GP counselling and nicotine patches	GP counselling	£ 345 per LYG (<35 years) to £ 785 (55-65 years)	€ 255 per LYG (<35 years) to € 579 (55-65 years)	- Design: decision analysis - Perspective: third-party-payer - Effectiveness: 12-month cessation rate counselling: 4.5%, nicotine replacement therapy: 9.6% (discount rate: 1.75%) - Costs: only intervention costs were included UK£ (price year: 1998) (discount rate: not relvant because of short term costs) - Sensitive to: changes in cost and effectiveness estimates (most for 12-month cessation rate and the cost of nicotine patches)

Table 7.5: Influenza vaccination of healthy working adults

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
Rothberg, 2005	US	Annual vaccination in healthy working adults	No vaccination	Cost-saving	NA	- Design: decision analysis. - Vaccination costs: US$239 (price year: 2001) - Vaccine efficacy: 72% (54-83%) - No discounting was applied, since the time-horizon was 1 year - Perspective: societal - Sensitive to: vaccination costs, annual probabilities of influenza and number of working days lost - Remarks: Amantadine therapy and rapid testing, followed by Oseltamivir antiviral therapy if the results are positive
Nichol, 2003	US	Vaccination in healthy working adults with live attenuated influenza virus vaccine (LAIV)	No vaccination (placebo)	Break-even cost of vaccination per person is: US$43.07	Break-even cost of vaccination per person is: €46	- Design: multi-center, randomized, double-blind, placebo-controlled trial - Vaccination costs: NS (price year: 1998) - Vaccine efficacy: NS - No discounting was applied, since the costs were incurred during 5 months - Perspective: societal - Sensitive to: hourly wage, productivity level when working at reduced effectiveness and relative rate of work loss among vaccinated versus unvaccinated person.
Lee, 2002	US	Vaccination in healthy working adults (18-50 years)	No vaccination	Vaccination has a higher net benefit than nonvaccination	NA	- Design: decision analysis - Vaccination costs: US$10.41 (price year: 2001) - Vaccine efficacy: 68% (50-86%) - No discounting was applied, since the costs were incurred during a short timeframe - Perspective: societal - Sensitive to: prevalence of influenza and number of working days lost
Das Gupta, 2002	UK	Annual vaccination (Influvac®) in healthy	No vaccination	Cost-saving (incidence ≥ 3.5%)	NA	- Design: decision analysis - Vaccination costs: £10.71 (price year: 2000)

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
		working adults (15-64 years)				- Vaccine efficacy: 68% (50-90%) - No discounting was applied, since the costs were incurred during a short timeframe - Perspective: employer - Sensitive to: incidence of influenza, and the cost of implementation of the programme
Nichol, 2001	US	Annual vaccination in healthy working adults (age 18-64 years)	No vaccination	Cost-saving	NA	- Design: decision analysis - Vaccination costs: US$10 (price year: 1998). - Vaccine efficacy in year with good match: 75% (60-90%) and in year with poor match 35% (0-50%) and likelihood of good vaccine match: 80% - Discounting: 3-5% (costs and benefits) - Perspective: societal - Sensitive to: influenza illness rate, absenteeism due to influenza and hourly wages
Campbell, 1997	US	Vaccination in healthy working adults (age 18-64 years)	No vaccination	Cost-saving	NA	- Design: prospective non-randomized, non-placebo-controlled trial - Costs for annual vaccination: US$45-47 - Vaccine efficacy: 24-59% - No discounting was applied, since the costs were incurred during a short timeframe - Perspective: societal - Sensitive to: is unclear, as there is no baseline calculation

Table 7.6: Pneumococcal vaccination of elderly persons

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
Baltussen, 1997	The Nether-lands	Vaccination against pneumococcal infections in people aged ≥ 55 years	No vaccination	1) Vaccination of people > 55 years: cost-effectiveness ratio of 3300 ECU per LYS 2) Vaccination of people > 65 years: cost-effectiveness ratio of 1500 ECU per LYS 3) Cost-saving for people > 85 years	1) Vaccination of people > 55 years: cost-effectiveness ratio of €4100 per LYS 2) Vaccination of people > 65 years: cost-effectiveness ratio of €1900 per LYS 3) NA	- Design: decision analysis - Vaccination costs: ECU 20.2 (price year: 1995) - Vaccine efficacy: 60% - Discount rate: 5% per annum for costs and benefits - Perspective: societal - Sensitive to: vaccine efficacy rate, duration of immunity hospital admission rate, costs of vaccine administration and retail price
Sisk, 1997	US	Vaccination against pneumococcal bacteremia in people aged ≥ 65 years	No vaccination	Vaccination turned out to be the dominant strategy	NA	- Design: decision analysis - Vaccination costs: US$12 (price year: 1993) - Vaccine efficacy: 90% for people 65-69 years and 65% for people >85 years (first year) - Discount rate: 3% per annum for costs and benefits - Perspective: societal - Sensitive to: vaccination costs, future medical costs of survivors, and vaccination effectiveness
De Graeve, 2000a	Belgium	Vaccination against pneumococcal infections in people aged ≥ 65 years	No vaccination	Cost-saving	NA	- Design: decision analysis - Vaccination costs: ECU 26.3 (price year: 1995) - Vaccine efficacy: 55% - Discount rate: 5% per annum for costs and benefits - Perspective: societal - Sensitive to: incidence rate and probability of hospitalization - Remark: it is assumed that the effectiveness of the vaccine holds for all pneumococcal

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
						pneumonia
De Graeve, 2000b	Belgium	Vaccination against pneumococcal infections in people aged ≥ 65 years	No vaccination	1) For people between 65-75 years the incremental cost-effectiveness ratio was ECU 24,872 per QALY (invasive disease) 2) Cost-saving for people > 65 years when assumed that vaccination prevents also noninvasive pneumonia	1) For people between 65-75 years the incremental cost-effectiveness ratio was €31,000 per QALY (invasive disease) 2) NA	- Design: decision analysis - Vaccination costs: ECU 22 (price year: 1995) - Vaccine efficacy: 86% for people 65-74 years and 62% for people >85 years (first year) - Discount rate: 3% per annum for costs and benefits - Perspective: societal - Sensitive to: effectiveness of the vaccination - Remarks: study also considered vaccination of adults between 18 and 64 years
Postma, 2001	The Nether-lands	Vaccination against pneumococcal bacteremia in people aged ≥ 65 years	No vaccination	10,100 Euro per LYG	€12,600 per LYG	- Design: decision analysis. - Vaccination costs: Euro 24.6 (price year: 1995) - Vaccine efficacy: 90% for people 65-69 years and 65% for people >85 years (first year) - Discount rate: 4% per annum for costs and benefits - Perspective: healthcare system - Sensitive to: effectiveness of the vaccination
Mukamel, 2001	US	Vaccination against pneumococcal bacteremia in people aged ≥ 65 years (Community Clinics Programme)	No vaccination	Vaccination turned out to be the dominant strategy	NA	- Design: decision analysis - Vaccination costs: US$98.95 (price year: 1998) - Vaccine efficacy: 86% for people 65-74 years and 62% for people >85 years (first year) - Discount rate: 3% per annum for costs and benefits - Perspective: societal - Sensitive to: effectiveness of the vaccination
Amazian, 2001	France	Vaccination against pneumococcal bacteremia in people	No vaccination	Cost-saving.	NA	- Design: decision analysis - Vaccination costs: FF 89 (price year: 1998) - Vaccine efficacy: 80% for people 65-74 years

First author, publication year	Country	Intervention scenario	Reference scenario	Original result economic evaluation	Converted result (2005 euros)	Characteristics economic evaluation
		aged ≥ 65 years				and 64% for people >85 years (first year). - Discount rate: 5% and 3% per annum for costs and benefits - Perspective: societal - Sensitive to: effectiveness of the vaccination and price of vaccination - Remark: in initial analyses the pneumococcal vaccine is assumed to be given at the same time as the flu vaccine
Melegaro and Edmunds, 2004	England and Wales	Vaccination against pneumococcal bacteremia in people aged ≥ 65 years alongside the influenza vaccine	Vaccination people that are at high risk of contracting an invasive pneumococ-cal infection	Vaccination turned out to be the dominant strategy	NA	- Design: decision analysis - Vaccination costs: £11.4 (price year: 2000) - Vaccine efficacy: 20% in high-risk group and 65% for the non high-risk group - Discount rate: 3% per annum for costs and benefits - Perspective: healthcare system - Sensitive to: vaccine efficacy rate
Mangtani, 2005	England and Wales	Vaccination against pneumococcal bacteremia in people aged ≥ 65 years	No vaccination	Cost-neutral: vaccine's efficacy would need to be 89% (with boosting) and 75% (without boosting). Assuming an efficacy of 37,5% (with booster) the cost are £8780 per LYS	Assuming an efficacy of 37,5% (with booster) the cost are €14,600 per LYS	- Design: decision analysis. - Vaccination costs: not specified (price year: 1999) - Vaccine efficacy: not specified (output variable) - Discount rate: costs: 6% and outcomes: 1,5% - Perspective: healthcare system/society - Sensitive to: incidence, case-fatality rates, and costs of illness - Remark: models are also estimated with inclusion of low efficacy against morbidity from pneumococcal pneumonia

Appendix 8: Transition probabilities and baseline prevalence numbers used in depression model

Table 1: Transition probabilities and baseline prevalence numbers for the different distinguished in the model

Non-depressed states	*Relapse probability**	*Baseline prevalence*	*Depressed states*	*Recover probability**	*Baseline prevalence*
0 - 3 weeks no symptoms	0.403	1542	0 - 3 weeks symptoms	0.448	1542
4 - 7 weeks no symptoms	0.070	1283	4 - 7 weeks symptoms	0.224	851
8 - 11 weeks no symptoms	0.042	1245	8 - 11 weeks symptoms	0.135	660
12 - 15 weeks no symptoms	0.030	1223	12 - 15 weeks symptoms	0.092	571
16 - 19 weeks no symptoms	0.023	1208	16 - 19 weeks symptoms	0.067	518
20 -23 weeks no symptoms	0.018	1197	20 -23 weeks symptoms	0.051	483
24 - 27 weeks no symptoms	0.015	1188	24 - 27 weeks symptoms	0.040	459
28 - 31 weeks no symptoms	0.013	1169	28 - 31 weeks symptoms	0.032	440
et cetera	0.012	1154	et cetera	0.027	426
	0.010	1141		0.022	415
	0.009	1129		0.019	405
	0.008	1118		0.016	398
	0.008	1109	> 1 year symptoms	0.014	27587
	0.007	1101			
	0.006	1093			
	0.006	1086			
	0.006	1079			
	0.005	1073			
	0.005	1068			
	0.005	1063			
	0.004	1058			
	0.004	1053			
	0.004	1049			
	0.004	1045			
	0.004	1041			
> 2 years no symptoms	0.003	305229			

*Probability over 4 weeks