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Economic evaluation of hepatitis B vaccination strategies

A systematic review of the literature

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Abstract

National and international economic evaluations of universal vaccination against hepatitis B were systematically selected from the literature. Only those studies were selected that had (a) reported original data in Dutch, English, French or German; (b) evaluated at least one universal vaccination strategy; (c) shown a high methodological quality and (d) been conducted in countries with a hepatitis B epidemiological pattern comparable to the Dutch situation. Sixteen relevant studies were identified out of 1060 publications registered in the databases COCHRANE LIBRARY, CURRENT CONTENTS, DARE, HEED, INAHTA DATABASE, MEDLINE, NEED and by applying the system of reference tracking. Despite the strict inclusion criteria, strong divergence is shown with regard to study assumptions, methodology, outcomes and conclusions. Some studies show universal screening to be cost-saving, while others report unfavourable cost-effectiveness ratios. Studies that investigated similar vaccination strategies reach dissimilar conclusions on the most cost-effective strategy. Several parameters were found to usually have a large impact on the results and conclusions of a study. These are: a) vaccine costs, b) discount rate, c) hepatitis B incidence, d) inclusion of indirect costs and effects, e) percentage of acute infections that lead to chronic hepatitis, f) discounting of effects and h) assumed lifelong costs of hepatitis B infection, including long-term consequences such as cirrhosis and liver cancer. Hence, in any further study these important variables should be subject to extensive sensitivity analysis. Economic evaluations that are intended to assist in local policy-making should take careful account of local circumstances. The 16 selected studies have little practical relevance for Dutch policy makers.

Preface

This study on the economic evaluation of hepatitis B vaccination strategies forms part of the RIVM project concerning the ‘efficiency of interventions in prevention and care’ and was performed at the department for Health Services Research CZO. The study is related to other RIVM projects on the epidemiology and the mathematical modelling of the transmission of infectious diseases performed at the department for Infectious Diseases Epidemiology CIE. The work on hepatitis B has been performed by order of the Ministry of Health, Welfare and Sports / Inspectorate for Health Care. With respect to the cost-effectiveness of interventions, CZO co-operates with the Institute for Medical Technology Assessment of the Erasmus University Rotterdam and this report is produced within the context of this co-operation. The study also forms part of the project on the ‘impact and costs of hepatitis B/C and HIV in intravenous drug users’ (CT.98.EP.06), funded by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).

Dr. J.C. Jager, projectleader

Contents

Samenvatting

Hepatitis is een leverontsteking die onder andere veroorzaakt kan worden door een virusinfectie, alcohol of drugs. Dit rapport gaat over de preventie van hepatitis die veroorzaakt wordt door het hepatitis B virus (HBV). Sinds 1986 is een vaccin beschikbaar dat geproduceerd wordt door middel van recombinant DNA technieken. Dit vaccin maakt bescherming tegen infectie mogelijk bij personen die nog niet eerder met het virus in aanmerking kwamen, en daarmee ook bescherming tegen de lange-termijn gevolgen van besmetting met het virus, zoals levercirrose en leverkanker. Het Hepatitis B virus kent heel verschillende verspreidingsvormen in verschillende regio's van de wereld. Nederland behoort, samen met andere West-Europese landen en Noord-Amerika, tot de laag-endemische gebieden. Rond de 5 procent van de bevolking komt tijdens het leven met HBV in aanmerking. Risico-groepen zijn onder anderen intraveneuze druggebruikers, dialysepatienten, homoseksuelen en personen met veel wisselende sexuele contacten. Zwangeren die drager zijn van het virus kunnen het virus tijdens of na de geboorte overgeven aan hun kind. Daarom worden zwangere vrouwen in Nederland sinds 1989 gescreend op aanwezigheid van het virus. Indien zij drager zijn worden hun kinderen onmiddellijk na de geboorte passief en actief geïmmuniseerd.

De Wereldgezondheidszorgorganisatie WHO beveelt sinds 1992 aan dat alle landen pasgeborenen vaccineren met het Hepatitis B vaccin. Dit is weliswaar kostbaar, maar op korte en lange termijn zouden daarmee ook kosten bespaard kunnen worden omdat minder mensen geïnfecteerd worden en ziekteverschijnselen ontwikkelen. Bovendien kan de ziektelast van Hepatitis B, in termen van voortijdige sterfte en verloren levensjaren, aanmerkelijk gereduceerd worden. In veel landen werden reeds economische evaluatiestudies uitgevoerd, ter ondersteuning van de besluitvorming rondom de invoer van dergelijke algemene vaccinatiecampagnes. Deze economische studies zijn gericht op het in kaart brengen van de kosten en effecten van vaccinatie op korte en (middel-)lange termijn.

In dit rapport wordt een overzicht gegeven van het "study design" en de uitkomsten van 16 gepubliceerde studies, die als onderwerp de economische aspecten van een of meerdere algehele vaccinatiestrategieën hadden. Deze studies zijn zorgvuldig geselecteerd uit een veel groter arsenaal van studies die handelen over economische aspecten van hepatitis B. Zeven verschillende databases werden geraadpleegd om relevante studies te identificeren: COCHRANE LIBERARY, CURRENT CONTENTS, DARE, HEED, INAHTA DATABASE, MEDLINE, NEED. Verder werd het systeem van "reference tracking" (sneeuwbalmethode) toegepast om nog niet eerder gevonden publicaties op te sporen. In drie tijdschriften die niet in bovenstaande databases zijn opgenomen en waarvan verwacht werd dat ze relevante bijdragen zouden kunnen bevatten werd handmatig gezocht. De volgende criteria werden gehanteerd voor de selectie van studies:

- oorspronkelijk werk over economische aspecten van hepatitis B preventie, waarin minimaal een algemene vaccinatiestrategie wordt geëvalueerd. De vaccinatiestrategie moet gericht zijn op een specifieke doelgroep, een regio of een land;
- Taal: Duits / Engels / Frans / Nederlands;
- Beschikbaar via Nederlandse bibliotheken;
- De studie moet uitgevoerd zijn in een land waar de epidemiologie van hepatitis B niet al te zeer afwijkt van de Nederlandse epidemiologische situatie. Een serum-prevalentie van 8 procent werd als bovengrens gehanteerd;
- De studie moet voldoen aan algemeen geaccepteerde methodologische richtlijnen voor economische evaluaties. De methodologische kwaliteit werd gekwantificeerd door middel van een lijst van 13 criteria, waarvoor 0 tot 4 punten verdiend konden worden. Studies waarvan het gemiddelde puntenaantal per van toepassing zijnd item 3 of hoger was werden geselecteerd voor deze literatuur review.

De diverse zoekstrategieën leverden 1060 referenties op. Daarvan kon een groot deel op grond van de opgestelde in-en uitsluitingscriteria onmiddellijk als niet relevant voor deze literatuurstudie worden aangemerkt. Een aantal van 84 artikelen en rapporten is wel gedegen bestudeerd. Een groot deel daarvan kon op basis van de kwaliteitscriteria terzijde worden gelegd. Uiteindelijk werden 16 studies geselecteerd voor dit literatuuroverzicht. Deze studies werden gepubliceerd tussen 1982 en 1998. Vijftien van de zestien studies werden echter in de jaren ’90 gepubliceerd. Van deze studies worden de volgende elementen systematisch beschreven in dit rapport:

- de onderzochte vaccinatiestrategie
- de doelgroep van het vaccinatieprogramma
- het land en regio waarin vaccinatieprogramma wordt uitgevoerd
- de incidentie van HBV in dat land / regio
- de serumprevalentie van hepatitis markers in dat land / regio
- diverse veronderstellingen omtrent de effectiviteit van het vaccinatieprogramma:
- de duur van de immuniteit na vaccinatie
- de werkzaamheid van het vaccin
- “compliance” met het vaccinatieprogramma
- het percentage van de doelgroep dat succesvol wordt gevaccineerd
- eventuele bijwerkingen van het vaccin
- het type economische evaluatie
- het perspectief van de studie
- de gebruikte modelleringstechniek(en)
- de duur van het vaccinatieprogramma
- de tijdshorizon voor het meten van effecten van het vaccinatieprogramma
- de tijdshorizon voor het meten van kosten en baten van het vaccinatieprogramma

- de veronderstelde kosten van het vaccin
- de bron die gebruikt wordt voor de kosten van het vaccin
- het basisjaar voor de kostencalculatie
- de munteenheid die gehanteerd wordt
- welke kostencategorieën worden meegenomen in de analyse
- de gehanteerde discontvoet
- het al dan niet disconteren van effecten
- welke variabelen worden onderzocht in een sensitiviteitsanalyse
- de variabelen die in de sensitiviteitsanalyse een belangrijke invloed op de resultaten van de studie blijken te hebben
- de gerapporteerde kosten-effectiviteits-ratio's
- de gerapporteerde baten-kosten-ratio's
- de conclusies die worden getrokken

Ondanks de toepassing van strikte selectiecriteria blijken de 16 geselecteerde studies sterk te verschillen qua onderzoeksmethodologie en ook qua rapportage. Sommige studies geven in uitvoerige bijlagen een zorgvuldige onderbouwing voor de keus van de parameterwaarden, andere studies refereren simpelweg aan gemaakte veronderstellingen in eerder gepubliceerde studies. De grootste verschillen tussen studies werden gevonden op de volgende terreinen:

- de veronderstelde duur van de immuniteit (tussen 3 jaar en levenslang)
- het percentage van de doelgroep dat bereikt wordt (tussen 26 % en 100 %)
- de gebruikte modelleringtechniek (eenvoudige berekeningen van vermeden infecties versus combinaties van Markov-keten-analyse en Monte Carlo simulatie met meenemen van "herd immunity" effecten)
- de duur van de interventie (van 1 tot 100 jaar)
- de tijdshorizon voor de berekening van effecten (van 1 tot 100 jaar)
- de tijdshorizon voor de berekening van kosten (van 1 tot 129 jaar)
- de veronderstelde kosten van het vaccin (US$ 6 tot US$ 225)
- het al dan niet includeren van indirecte kosten (productiviteitskosten)
- het al dan niet disconteren van effecten van vaccinatie
- de gebruikte discontovoet (van 0 tot 8 %)

Vanwege deze enorme verschillen is het moeilijk om de in de diverse studies getrokken conclusies rechtstreeks met elkaar te vergelijken. De conclusies zijn dan ook heel verschillend: sommige studies concluderen dat algemene vaccinatiecampagnes kostenbesparend zouden kunnen worden georganiseerd, andere studies rapporteren juist extreem hoge kosten-effectiviteits-ratio's. Studies waarin meerdere vaccinatiestrategieën met elkaar worden vergeleken trekken verschillende conclusies omtrent de meest kosten-effectieve strategie: soms is dat de algehele vaccinatie van pasgeborenen, soms een op adolescenten gerichte strategie en soms combinaties van beide strategieën. De twee studies waarin vaccinatiecampagnes gericht op mannelijke homoseksuelen en intraveneuze druggebruikers worden geëvalueerd conclude-

ren dat het waarschijnlijk mogelijk is om dit kosten-neutraal of zelfs kostenbesparend te doen. Vanwege de enorme verschillen tussen studies is het in ieder geval niet mogelijk om conclusies die getrokken worden in een bepaalde setting rechtstreeks naar een andere setting te vertalen. Elke beleidsbeslissing die genomen moet worden omtrent het al dan niet invoeren van algemene vaccinatie tegen hepatitis B vereist een zorgvuldige studie waarin de locale omstandigheden zo gedetailleerd mogelijk worden meegenomen. De geselecteerde studies hebben in het algemeen dan ook weinig praktische relevantie voor in Nederland te nemen beleidsbeslissingen.

Omdat de studies zo sterk verschillen is het belangrijk dat de invloed van de keuze van parameterwaarden op het eindresultaat van de studie zichtbaar gemaakt wordt. Alle studies besteden hieraan aandacht in min of meer uitgebreide sensitiviteitsanalyses. De volgende parameters worden het meest genoemd als belangrijke beïnvloeders van de uitkomsten van de studies:

1. De kosten van het vaccin
2. De gehanteerde discontovoet
3. De incidentie van hepatitis B
4. Het al dan niet meenemen van indirecte kosten/effecten
5. Het percentage infecties dat resulteert in een chronische besmetting met HBV
6. Het al dan niet disconteren van effecten
7. De veronderstelde levenslange kosten van hepatitis B besmetting, inclusief lange termijn gevolgen zoals levercirrose en leverkanker

Het verdient aanbeveling dat in toekomstige economische evaluaties in elk geval de invloed van bovenstaande variabelen gedetailleerd wordt onderzocht.

Summary

Hepatitis is an inflammation of the liver that may be caused by a variety of agents including viruses, alcohol and drugs. This report focuses on the prevention of hepatitis that is generated by the hepatitis B virus (HBV). A vaccine against HBV that is produced using recombinant DNA technology is available since 1986. It enables the protection of persons that have not yet been infected by the virus. It also prevents long term complications of HBV-infection such as cirrhosis and liver cancer. The predominant modes of HBV transmission vary throughout the world. With other European countries and the US, the Netherlands belongs to countries with low HBV endemicity. Some 5% of the inhabitants of the Netherlands will become infected with HBV during their lifetime. Intravenous drug users, dialysis-patients, homosexuals, and people with many different sex-partners are at increased risk for HBV infection. Infected pregnant women can transfer the virus during birth (vertical or perinatal transmission). Because of that, pregnant women are screened for HBV in the Netherlands since 1989. If they are HBV-carrier their offspring will receive active and passive immunisation.

Since 1992 the World Health Organisation recommends that worldwide all newborns should be vaccinated with the hepatitis B vaccine. This is expensive, but sooner or later medical expenditures will be prevented, as fewer persons are infected and develop disease symptoms. Furthermore, the burden of hepatitis B, in terms of premature deaths and loss of life-years can be reduced significantly. In many countries, economic evaluation studies have been conducted to support decision making about the implementation of such vaccination programmes. These economic studies are aimed at the investigation of costs and effects of vaccination on the short, (middle) and long term.

In this report we present an overview of the study design and results of 16 published studies that examine the economic aspects of one or several universal vaccination strategies. These studies have carefully been selected from a much bigger pool of studies that are concerned with the economic aspects of hepatitis B. Seven different databases have been searched to identify the relevant studies: COCHRANE LIBRARY, CURRENT CONTENTS, DARE, HEED, INAHTA DATABASE, MEDLINE, NEED. In addition, the system of reference tracking was used to find publications that were not covered in these databases. Finally, the indexes of three journals that were expected to contain relevant papers and were known not to be indexed in the databases used were searched manually. The following criteria have been used to select the studies:

- Original study about the economic aspects of hepatitis B prevention that evaluates minimally one universal vaccination strategy. The vaccination strategy has to be aimed at a specific target population, a region or a country;
- Language: Dutch, English, French, German;
- Available from Dutch libraries;

- The study has to be conducted in a country in which the epidemiology of hepatitis B differs not too much from the Dutch epidemiological situation. A serum prevalence of 8 percent has been used as upper limit for this criterion;
- The study has to follow commonly accepted methodological guidelines for economic evaluations. The methodological quality is quantified by employing a list of 13 criteria. For each criterion points were given, from 0 (low quality) to 4 (high quality). Only studies that reached an average score of 3.0 or higher were selected for this literature review.

The various search strategies resulted in 1060 references. The majority of these studies could be identified as not relevant by applying the above described inclusion / exclusion criteria. Most of the remaining 84 studies did not meet the high methodological standards required. Finally, 16 studies were selected for the literature review. These studies have been published between 1982 and 1999. Fifteen of the sixteen studies are even published in the 1990s. The following elements of these studies are systematically described in the report:

- Investigated vaccination strategy
- Target population of the vaccination programme
- Country and region of study
- Incidence of HBV in that country or region
- Serum-prevalence of hepatitis B markers in that country or region
- Some assumptions about the effectiveness of the vaccination programme:
- Duration of immunity after vaccination
- Vaccine-efficacy
- Compliance with the vaccination programme
- Percentage of the target population that is successfully vaccinated
- Possible side-effects of the vaccine
- Type of economic evaluation
- Study-perspective
- Applied modelling technique(s)
- Duration of the vaccination programme
- Time-horizon for measuring effects of the vaccination programme
- Time-horizon for measuring costs and benefits of the vaccination programme
- Assumed costs of the vaccine
- Sources of the vaccine cost data
- Basic year for the cost-calculation
- Currency unit
- Included cost categories
- Discount rate
- Discounting of effects
- Variables investigated in the sensitivity analysis

- Variables that were identified in the sensitivity analysis to influence the results significantly
- Presented cost-effectiveness ratios
- Presented cost-benefit ratios
- Conclusions

Despite the application of strict selection criteria, the 16 selected studies diverge with respect to their methodology and reporting. Some studies supply with comprehensive information and a solid basis for the chosen parameter values. Other studies simply refer to the assumptions that have been made in the literature. The biggest differences between the 16 studies have been observed in the following topics:

- Assumptions on the duration of the immunisation (between 3 years and life-long immunity)
- The percentage of the target population that can be reached (between 26 and 100%)
- Applied technique for modelling (simple calculation of averted infections versus combinations of Markov-chain-analysis and Monte Carlo simulation considering herd immunity effects)
- Duration of the intervention (1 to 100 years)
- Time horizon for the cost calculation (1 to 129 years)
- Assumed vaccine costs (US$ 6 to US$ 225)
- whether or not indirect costs (productivity costs) were included
- whether or not effects were discounted
- Discount rate (0 – 8%)

Because of these big differences it is difficult to compare the conclusions of the selected studies. Also, conclusions reached are sometimes contradictory: some studies point out that universal vaccination may be cost saving while others report unfavourably high cost-effectiveness ratios. Studies that investigate several vaccination strategies reach dissimilar conclusions regarding the most cost-effective strategy. Some studies suggest universal vaccination of new-borns is most cost-effective. Others show that vaccination of adolescents has the lowest cost-effectiveness ratio. Finally, there are also studies that favour a combination of both strategies. Two studies were conducted to evaluate HBV-vaccination of homosexual men and intravenous drug users. They reach the conclusion that these programmes are likely to be cost-neutral or even cost saving. Due to the enormous differences between the studies it is not easy to apply conclusions that have been reached in one particular setting also in another setting. Any policy-decision about the introduction of universal HBV screening requires a careful analysis. The local circumstances should be taken into account as close as possible. Thus, the selected studies generally have little relevance for policy making in the Netherlands.

As the selected studies differ so much it is important to show the influence of parameter values on the study results. For this, all studies employ sensitivity analyses. The following parameters have most often been identified as sensitive variables:

1. Vaccine costs
2. Discount rate
3. Hepatitis B incidence
4. Exclusion of indirect costs / effects
5. Percentage of infections that lead to chronic HBV infections
6. Not discounting of effects
7. Assumed lifelong costs of HBV infection, including long-term consequences such as cirrhosis and liver cancer

It should be noted that in future economic evaluations the influence of the factors above should always be investigated in detail.

1. Introduction

This report describes the results of a literature review on the economic attractiveness of general vaccination programs directed at limiting the burden of hepatitis B to society. In Chapter 2, the reader will be introduced to the disease and its causes, the epidemiological patterns as found in various regions of the world and in the Netherlands in particular, and to several strategies to prevent hepatitis B. Chapter 3 contains a description of the aim and conduct of the literature review. In- and exclusion criteria, the search strategy and databases that were consulted are described. Chapter 4 contains the results of the study. Firstly, the result of the selection process is explained. Secondly, the main characteristics of the 16 selected studies are described in a systematic way. In Chapter 5, general observations and a discussion of the results of the study can be found. Several Appendices provide with background material to the study.

2. Background

2.1 Hepatitis B virus

Hepatitis is a general term for an inflammation of the liver that may be caused by viruses, bacteria, drugs, toxins, metabolic disease or excess alcohol intake. Individuals with hepatitis tend to have generalised symptoms that resemble symptoms of the early stages of flu, such as fatigue, nausea, fever, diarrhoea and jaundice. As the disease progresses, other symptoms may occur: chills, weight loss, distaste for food, extreme fatigue, pain in the right upper quadrant and dark urine. It is only since 10 years that the 5 different viruses (hepatitis A, B, C, D and E) that are currently known to cause viral hepatitis may be distinguished. Hepatitis A and B have been known since the 1940s. The other three viruses have been identified in the 1970s and late 1980s. Because symptoms are not specific to the causative agent, it is impossible to base a diagnosis on clinical symptoms alone. Serological testing is required. This report is only concerned with hepatitis B (formerly “serum hepatitis”), the hepatitis virus that has most serious health consequences.

HBV is transmitted by infected blood and other body fluids, e.g. semen and vaginal secretions. Perinatal, horizontal (e.g. household-contacts), sexual, and parenteral (e.g. skin penetration with contaminated medical, dental, tattooing or piercing devices) transmission ways are currently recognised. Risk groups include injecting drug users, persons with multiple sex partners or a history of sexually transmitted diseases, health care workers who have occupational contact with blood, haemodialysis patients, infants born to HBV infected mothers, institutionalised populations, recipients of unscreened blood or blood-derived products and household contacts of HBV infected individuals.

To identify HBV and to determine the status of an HBV-infection, serologic markers of HBV are used. Among them are hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg), hepatitis B e antigen (HBeAg) and the corresponding antibodies. The laboratory criteria for diagnosis of an acute HBV infection are 1) presence of HBsAg or IgM antibody to HBcAg, and 2) absence of IgM anti-hepatitis A antigen. HBsAg indicates active viral replication and shows that a person is infectious. HBsAg presence for 6 months or a positive test for HBsAg with a negative test for IgM anti-HBc indicates that the chronic carrier state has developed. HBeAg is positively associated with the risk of transmission. Mothers who are positive for HBsAg and HBeAg have a risk of 0.7 to 0.9 to infect their newborn baby perinatally [Beasly, 1981]. If a mother is positive for HBsAg but negative for HBeAg, the risk of perinatal transmission is reduced to 0.2 or less.

HBV causes acute and chronic hepatitis. The chances of becoming chronically infected depend upon age. About 90 percent of infected neonates and 30-50 percent of infected small children will become chronically infected. [Edmunds, 1993] In contrast, 10 to 15 % of adolescents and 2 to 8 % of adults infected with HBV develop chronic hepatitis B. In some individuals who become chronically infected, especially neonates and children, the acute infection will not be clinically apparent. Acute hepatitis can range from subclinical disease to fulminate hepatic failure. Patients with chronic HBV are potentially infectious, may have clinically apparent chronic hepatitis and are at risk for developing cirrhosis (necrosis of liver cells) and primary liver cancer (hepatocellular carcinoma or HCC).

2.2 Epidemiology

The hepatitis B virus is carried by an estimated 2 to 3 billion people in the world, and is the major cause of liver cancer. [Blumberg, 1975] Hepatitis B ranks second only to tobacco smoking as a cause of global cancer mortality. Hepatitis B is characterised by different epidemiological patterns in different regions of the world. Overall, incidence is lowest in Western Europe and other developed countries and highest in Asian countries. Within Europe, 3 different types of hepatitis B epidemiological patterns may be distinguished, based on different chronic HBsAg carriage rates. [Goudeau, 1990] In general, the level of endemicity increases from north to south and from west to east. The 3 different types are shown in Table 1.

Table 1: Epidemiological patterns of hepatitis B in Europe

Characteristics	Country		
	Type 1	Type 2	Type 3
Overall prevalence of markers	< 5 %	5 - 10 %	10 - 20 %
Prevalence of HBsAg	< 0.1 %	0.1 – 5 %	North Europe: 0.5 % South Europe: 5 %
Main transmission route	None	Sexual	Perinatal or at young age
Transmission from HBsAg + mothers	None	± 1 % of births	± 3 % of births

Source: Goudeau, 1990

In typical type 1 countries, incidence of hepatitis B has always been low and is further declining as a result of successful immunisation of high-risk groups, such as health care workers and intravenous drug users. In type 2 countries, sexual transmission is the primary source of infection. Some type 2 countries have been able to reduce the perinatal transmission by means of screening of pregnant women. In type 3 countries, incidence occurs mostly before the age of 5 years, during birth or within families (household contacts).

The Netherlands may be characterised mainly as a type 2 country, although the introduction of prenatal screening (in 1989) has reduced the percentage of new-borns with HBV infection significantly. In 1989-1990, hepatitis B prevalence (HBsAg +) among pregnant women was 0.45 %. [Grosheide, 1991] Recent research showed that 2.1 % of the Dutch population had markers of current of past HBV infection and that the serum-prevalence of HBsAg was 0.2 %. [van Marrewijk, 1999] Annual incidence of acute hepatitis B, as reported to the Inspectie voor de Gezondheidszorg (Inspectorate for Health Care) is about 1.45 cases per 100.000 of the population. [Grosheide, 1991] The incidence among males is about 2.3 times higher than among females. Incidence occurs most in persons between 15 and 44 years of age. However, these incidence data are unreliable due to inadequate diagnosis and reporting of hepatitis B infection.

2.3 Prevention

Spread of the infection may be prevented through the screening of blood and blood products, adequate sterilisation of medical equipment, destruction of disposables, effective use of barrier techniques (condoms, gloves) and education about the disease and its risk factors. Temporary passive prophylaxis is available through the Hepatitis B Immune Globuline (HBIG). Its immediate use is recommended for infants born to HBV infected mothers, sex partners of individuals with acute hepatitis B, and in unvaccinated health care workers who experienced a needle stick injury. Post-exposure prophylaxis with HBIG is advocated along with the hepa-

titis B vaccine, which offers active and prolonged immunity. The first hepatitis B vaccine available (1982) was produced from the plasma of persons chronically infected with HBV. The vaccines that are being used since 1985 are produced by recombinant DNA technology. The conventional regimen is a series of three intramuscular doses given over a six-month period: initial vaccination, again at 30 days and at 6 months. This regimen induces antibody re-sponse (measured as the persistence of anti-HBs in serum) in 85-90 percent of adults and in over 95 percent of infants and children. The persistence of anti-HBs in serum is related to the peak antibody response immediately after vaccination, but protection against clinical disease or development of the carrier state lasts long after detectable antibody has disappeared. The duration of protection is unknown, present evidence indicates a period of at least 10-15 years. [Coursaget, 1994] In 1992, the World Health Organisation has recommended that universal hepatitis B vaccination should be integrated into national immunisation programmes in all countries by 1997. [Van Damme, 1997] Countries of high and intermediate endemicity, with rather uniform patterns of infection in new-borns and small children, have been more apt to implement such policies than countries of low endemicity. Within Europe, some countries (e.g. Italy, France) with relatively high incidence and prevalence of hepatitis B have initiated infant, adolescent, or combined vaccination programmes. Other countries remain unconvinced that such universal vaccination campaigns are justified.

In the Netherlands, prenatal screening of pregnant women has been in effect since 1989. [Grosheide, 1991] Women are tested early in pregnancy for HBsAg status. If the mother is identified as HBsAg positive, the infant is given HBIG immediately after birth, along with a series of three doses of vaccine. In 1983, the Health Council of the Netherlands issued an advice on prevention of hepatitis B, which advocated vaccination of high-risk groups. [Gezondheidsraad, 1983] In a more recent advice of the Health Council, [Gezondheidsraad, 1996] it is concluded that this policy of selective vaccination of high-risk groups has only been partially successful. The execution of the high-risk vaccination programme has been good with regard to haemodialysis patients, haemophiliacs, medical and dentistry students, moderate with regard to institutionalised persons, new-born babies of HBsAg-positive mothers, persons who experienced needle-stick accidents and health care workers in general, and unsatisfactory with regard to sexual partners of infected individuals, male homosexuals, prostitutes and intravenous drug users. The Health Council considered insufficient funding and the lack of clearly defined responsibility for the enforcement of the policy as the main reasons for the failing immunisation policy directed at high-risk groups. In his 1996 advice, the Health Council urged a more active and intensive policy to prevent spread of HBV. In addition to the high-risk groups defined in the 1983 report, some new groups were defined, such as visitors of clinics for sexually transmitted diseases and individuals with Down’s Syndrome. The Council recommended taking steps to prepare the implementation of a general immunisation programme against hepatitis B, provided that such a general immunisation programmecould be incorporated in the Netherlands’ National Immunisation Programme and that the cost of vaccine should be acceptable.

3. Design and conduct of literature review

3.1 Aim of the literature review

This literature review is being done within the framework of RIVM project 403505 “Doelmatigheid van interventies in zorg en preventie” (Efficiency of interventions in prevention and care). Besides, a cost-effectiveness analysis (CEA) of several vaccination strategies to prevent spread of hepatitis B in the Netherlands is also being conducted within RIVM project 403505. Within the literature, many publications on this topic can be found. Separate analyses have been reported for many different countries and populations (risk-groups). The purpose of the current literature review is to gain insight in methods and outcomes of previously published economic evaluations of such vaccination policies. A second purpose is to gain insight into the relevance of previous research for the current Dutch discussion on the necessity of general vaccination. This merits a limitation of the review to studies that have been performed in countries where the epidemiology of hepatitis B is comparable to epidemiological patterns as found in our country. If necessary, the design and conduct of the ongoing cost-effectiveness analysis may be adjusted to findings of the literature review.

3.2 Design of the literature review

3.2.1 Criteria for selection of papers

Papers for the initial phase of the literature review were selected according to the following characteristics:

- Original work on economic evaluation of hepatitis B prevention strategies, including at least one general vaccination strategy targeted at a specific risk group, a region or a country
- Language: Dutch /English /French/German
- Available from Dutch libraries
- Since it is self-evident that there is a clear relationship between cost-effectiveness of any vaccination campaign and the prevalence of the disease, the work must be done in a country where epidemiology of hepatitis B is not too different from epidemiology of hepatitis B in the Netherlands. If details on serum-prevalence were given in the report under study, a serum-prevalence of 8 % was used as the upper limit for inclusion of a study in this review.

- Sufficient quality. For each study, a quality rating was completed, according to Bradley *et al*. and Sacristan *et al*. [Bradley, 1995; Sacristan, 1993] This checklist is based on widely accepted standards of economic evaluation methodology, [Drummond, 1997] but has the additional advantage of composing a numerical score for the quality of the paper. Studies with an average quality rating ≥ 3 per applicable item were selected for the current review. The quality rating form is included in Appendix 2.

We thus excluded review articles, studies concentrating on passive immunisation and/or screening only, and studies that presented insufficient data to assess the merits of the study, such as short reports and abstracts. The reason for exclusion was documented with all excluded papers. Cost-of-illness studies were excluded from this review as well. Studies that focused only on cost-effectiveness issues within a micro context (i.e. whether or not to implement vaccination in one specific hospital) were also considered irrelevant for the current review.

3.2.2 Databases used to identify relevant publications

Papers for the initial phase of the literature review were selected using the following databases:

1. COCHRANE LIBRARY.

This database includes published reviews and is maintained by the Cochrane Collaboration and is available on CD-ROM (1998 4th Issue).
The following search strategy was used: hepatitis B.

2. CURRENT CONTENTS (All scientific editions from 1996 until January 1999).

This database was used because it contains information from important journals that were known not to be indexed in MEDLINE, such as *European Journal of Public Health, Medical Care* and *PharmacoEconomics*.
The following search strategy was used:
Hepatitis B WITH
Econom* OR
Cost*.

3. DARE (Database of Reviews of Effectiveness).

This database is maintained by the National Health Service Centre for Reviews and Dissemination, University of York, and is accessible through Internet. The database includes published reviews.
The following search strategy was used: Hepatitis B.

4. HEED (Health Economic Evaluation Database)
This database is maintained by the Office of Health Economics of the Department of Health and Social Security (London) and is accessible through CD-ROM.
The following search strategy was used: hepatitis.

5. INAHTA DATABASE.
The International Network of Agencies of Health Technology Assessment (INAHTA) maintains a database of publications by its member organisations. This database is accessible through Internet.
The following search strategy was used: hepatitis B.

6. MEDLINE (from 1966 until December 1998).
MEDLINE is maintained by the United States National Library of Medicine and can be accessed through the Internet.
The following search strategy was used:
Hepatitis B (all subheadings) WITH
Costs and Cost-Analysis (all subheadings) OR
Health care Economics and Organisation (all subheadings) OR
Economics (all subheadings).

7. NEED (NHS ECONOMIC EVALUATION DATABASE).
This database is also maintained by the NHS Centre for Reviews and Dissemination, University of York, and is accessible through Internet. The database includes standardised descriptions of published studies. The following search strategy was used: hepatitis.

Furthermore, six reviews on economic aspects of hepatitis B vaccination were identified. [Jefferson, 1994; Demicheli, 1997; Jefferson, 1998, Holliday, 1994; Badia, 1997, Beutels, 1998]. These reviews have been checked to identify further economic studies.

3.2.3 Further procedures

In the initial phase of the literature review, the selected papers were read. For those studies with an average quality rating ≥ 3 per applicable item, two other forms were completed:

- "parameter estimate" form. This form was designed to enable a more precise estimation of key parameters in the Dutch CEA of HBV prevention strategies. This form only needed completion for those parameters that were also applied in the study under review. Appendix 3 shows this parameter estimate form.
- "study characteristics" form, to enable a systematic description of each selected study in this literature review. This form can be found in Appendix 4.

The reviewer wrote a short report on the study, including both a factual description of study characteristics and a more qualitative assessment of advantages and disadvantages of the study design and conduct as chosen in the study under review. These short reports are included in Appendix 5. To enable reference tracking afterwards, relevant references were marked in the paper. If those publications had not been identified before, they were read and it was assessed whether the study should be included or not.

4. Results

4.1 Results of selection process

The search strategies as described in paragraph 3.2. provided with a total number of 1060 entries. For the majority of these entries, it was immediately clear that no further action needed to be taken because one or more exclusion criteria applied, for instance because the publication concerned a letter, editorial comment or economic evaluation of treatment of hepatitis B or screening only. After this first selection process, 84 publications survived for a more detailed assessment. These publications have all been read carefully and a quality assessment was made. The majority of the papers selected in this phase of the review could not meet with the high methodological standards that were used for the economic evaluation methodology, did not meet all inclusion criteria or did fulfil exclusion criteria. The excluded studies are listed in Appendix 6. Finally, 16 papers fulfilled all requirements and were selected for further investigation. These 16 papers are described in more detail in Appendix 5 and summarised systematically in the following paragraphs.

4.2 Main characteristics of 16 selected papers

4.2.1 Vaccination strategy

Table 2 shows the different vaccination strategies and target populations that are described in 16 selected papers.

Table 2: Vaccination strategies and target populations as studied in 16 selected papers

First author	Year of publication	Vaccination strategy	Target population
Mulley	1982	General vaccination	Homosexual men
		Screen + vaccinate	Surgical residents
		Passive immunisation	General US population
Ginsberg	1992a	General vaccination	All neonates
		Doing nothing	
Ginsberg	1992b	General vaccination	All under-16-year-olds
			All neonates
Demicheli	1992	General vaccination	All neonates + 12 years 'catch-up' of 12 year-olds
Bloom	1993	General vaccination	All neonates
		Screen + vaccinate	10-year-olds
		Doing nothing	High-risk adults
			General adult population
			Mixes of these 4 populations
Krahn	1993	Screen + vaccinate	All neonates
		Screen + vaccinate + universal vaccination of new-borns	
		Doing nothing	
Oddone	1993	General vaccination	Pre-dialysis patients
		Doing nothing	Patients starting dialysis
Eelkman Rooda	1994	Screen + vaccinate	All neonates
		General vaccination	All neonates + 10 years 'catch-up' of 10 year-olds
		Doing nothing	
Margolis	1995	Screen + vaccinate	All neonates
		Screen + vaccinate + universal vaccination of new-borns	11-13-year-olds
		Screen + vaccinate + universal vaccination at 11-13 years of age	
Antoñanzas	1995	General vaccination	12-year-olds
		Screen + vaccinate + general vaccination	neonates
			Combinations of 2 groups
Kerleau	1995	General vaccination	General population
		Screen + vaccinate	15-40 year-old males
		Doing nothing	Male homosexuals
			Drug users
Fenn	1996	General vaccination	Neonates
			6-year-olds
			11-year-olds
			Neonates + 11-year-olds

First author	Year of publication	Vaccination strategy	Target population
Beutels	1996	General vaccination Doing nothing	All neonates 12-year-olds All neonates + 12 years 'catch-up' of 12 year-olds
Garuz	1997	Screen + vaccinate General vaccination	All neonates 12-13-year-olds All neonates + 'catch-up' of 12-13-year-olds
Wiebe	1997	Screen + vaccinate + general vaccination	All neonates 10-year-olds 12-year-olds
Krahn	1998	General vaccination Screen + vaccinate + high-risk individuals	12-year-olds Neonates

Table 2 shows that the majority (13 out of 16) of selected studies at least describe the results of neonatal vaccination strategies. Several studies combine this strategy with the strategy of screening of pregnant women and selective vaccination of their offspring, because this was the major preventive strategy in a country, before general vaccination was considered. Eleven studies describe results of adolescent vaccination campaigns. Only three studies were directed at specific risk-groups, such as drug users or male homosexuals.

4.2.2 Country of study and its epidemiological pattern of HBV spread

Table 3 provides information on the country or region where the study was performed, along with its epidemiological pattern of HBV transmission, according to the authors of the papers. The incidence data are in general calculated data, based on more or less sound assumptions on the percentage of underreporting of hepatitis B.

Table 3: Country of study and epidemiological data

First author	Year of publication	Country, region	Incidence / 100.000 population	Prevalence of markers
Mulley	1982	United States	100	5 – 10 %
Ginsberg	1992a	Israel	270	[a]
Ginsberg	1992b	Israel	270	[a]
Demicheli	1992	Italy	30	[a]
Bloom	1993	United States	115	4.8 %
Krahn	1993	Canada & United States	[a] (300.000 infections per year)	[a]
Oddone	1993	United States	200 [b]	[a]
Eelkman Rooda	1994	Netherlands	[c]	[a]
Margolis	1995	United States	[a]	4.8 %
Antoñanzas	1995	Catalonia, Spain	150	[a]
Kerleau	1995	France	100	5 – 10 %
Fenn	1996	United Kingdom	12.6	[a]
Beutels	1996	Flanders, Belgium	20 – 500 [c]	7.6 %
Garuz	1997	Spain	[a] (60.000 infections per year)	[a]
Wiebe	1997	Manitoba, Canada	19	[a]
Krahn	1998	British Columbia, Canada & USA	30 (British Columbia)	[a]

[a] not given

[b] risk-group specific incidence

[c] depends on age-group, no overall figure given

It appears from table 3 that, despite the *a priori* selection of studies from countries with low or intermediate endemicity, large differences in reported or calculated incidence rates appear between the studies. Some studies do not report on the epidemiological background at all. Only very few studies have been done in countries where the epidemiological pattern of hepatitis B is really comparable with the Dutch epidemiological pattern. This hampers the direct comparison of study results between the selected studies.

4.2.3 Variables considering the vaccination program

Table 4 shows the different assumptions that have been made on:

1. the duration of immunity after successful vaccination;
2. the efficacy of the vaccine (after a completed cycle of 3 vaccinations);
3. the compliance with the vaccination program;
4. the percentage of the target population that is successfully vaccinated by the vaccination program;
5. whether a booster vaccination was assumed and if so, after how many years;
6. whether adverse effects of the vaccine were included in the study.

Table 4: Assumptions on effectiveness of vaccination program (for explanation of numbers see above)

First author	Year of publication	1.	2.	3.	4.	5.	6.
Mulley	1982	5 years	87.5 %	100 %	87.5 %	-	yes
Ginsberg	1992a	5 years [a]	95 %	100 %	95 %	-	yes
Ginsberg	1992b	5 years [a]	95 %	95 %	90.25 %	-	yes
Demicheli	1992	life-time	100 %	100 %	100 %	-	no
Bloom	1993	life-time	80-90 % [b]	33-70 % [b]	26-63 % [b]	10 + 20	no
Krahn	1993	decreasing annually [c]	90 %	90 %	81 %	-	yes
Oddone	1993	3 years	55-80 % [d]	100 %	55-80 %	-	no
Eelkman Rooda	1994	life-time	100 %	100 %	100 %	-	no
Margolis	1995	6-13 years	95-100 %	40-60 %	69 %	-	no
Antoñanzas	1995	life-time	90-95 %	68-90 %	61-86 %	10	no
Kerleau	1995	5 years	95 %	100 %	95 %	-	no
Fenn	1996	5 years	90 %	100 %	90 %	5	no
Beutels	1996	35 years	95-99 %	80-90 %	76-89 %	-	no
Garuz	1997	10 years + life-time	90 %	68-90 %	61-81 %	10	no
Wiebe	1997	decreasing annually [c]	90 %	90 %	81 %	-	yes
Krahn	1998	decreasing annually [e]	99 %	94 %	93 %	-	no

[a] efficacy of vaccine declining by 15 % every 5 years, so efficacy is 80.75 % after 10 years, 68.64 % after 15 years, et cetera

[b] depending on target population

[c] by 2-8 %

[d] lower response rate because of diseased target group

[e] by 4.5 %

Table 4 shows convincingly that the 16 studies have made quite different assumptions on the effectiveness of the vaccination programs. For instance, evidence on the duration of the protective effect of vaccination is still lacking, because the recombinant vaccine was only introduced in 1986. With respect to the duration of immunity after successful vaccination, some studies make a very conservative assumption of 3-5 years protection, while others assume lifetime immunity. Several studies tried to handle the uncertainty by way of modelling annually decreasing immunity levels. The fourth column of table 4 shows the overall effectiveness of the program, which is a product of assumptions on vaccine efficacy and compliance with the program. Depending on the target population, percentages as low as 26 % and as high as 100 % have been found.

4.2.4 Type of economic evaluation and perspective of study

There are three major types of economic evaluation that consider both costs and effects of a technology. These are cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA).

- In a CEA, competing interventions are compared in terms of cost per unit of consequence, usually life-years gained or cases of HBV infection averted.
- A CUA design enables the measurement of effects on both quantity and quality of life. Competing interventions are compared in terms of cost per unit of utility gained, usually cost per Quality-Adjusted-Life-Year (QALY).
- In a CBA, all costs and benefits of health care programs are measured in monetary units. Hence, a CBA requires monetary valuation of quality of life outcomes, which is a rather difficult task [Drummond, 1997]. Some studies that omit the effects on quality of life are labelled as a CBA, but are in fact CEAs. The two selected Ginsberg studies are good examples for this type of mislabelling.

In table 5 an overview of the economic evaluation study design in the selected studies is given, along with the perspective that was taken for the evaluation. The application of strict selection criteria for our review did not allow for a study to take a micro perspective only, such as economic effects for one hospital. Therefore, two major perspectives remain: the societal perspective and the third-party-payer perspective (including a national health services perspective).

Table 5: Type of economic evaluation and perspective of the evaluation

First author	Year of publication	Type of economic evaluation	Perspective taken
Mulley	1982	CEA	Third-party payer
Ginsberg	1992a	CEA	Societal
			Third-party payer
Ginsberg	1992b	CEA	Societal
			Third-party payer
Demicheli	1992	CBA	Societal
Bloom	1993	CEA	Third-party payer
Krahn	1993	CEA	Societal
			Third-party payer
Oddone	1993	CEA	Third-party payer
Eelkman Rooda	1994	CEA	Societal
Margolis	1995	CEA	Societal
Antoñanzas	1995	CEA	Third-party payer
Kerleau	1995	CEA	Third-party payer
Fenn	1996	CEA	Third-party payer
Beutels	1996	CEA	Societal
			Third-party payer
Garuz	1997	CEA	Third-party payer
Wiebe	1997	CEA	Third-party payer
Krahn	1998	CEA	Societal
			Third-party payer

Table 5 makes clear that CEA is the study design that is applied most often. As mentioned before, the two Ginsberg studies represent also CEAs despite the fact that their authors call them CBAs. Only one CBA and no CUA were selected. The majority of the studies at least reported results from a third-party payer perspective, either a health insurance or a national health services system. Half of the studies also took a societal perspective and tried to incorporate all costs and effects of interventions on a societal level, irrespective of the paying or benefiting institution.

4.2.5 Modelling techniques

The different studies have used different techniques to model the effectiveness of the intervention under survey. Table 6 provides with an overview of this aspect of the selected studies.

Table 6: Modelling technique(s) used in selected studies

First author	Year of publication	Modelling technique(s)
Mulley	1982	Decision analysis
Ginsberg	1992a	Decision analysis
Ginsberg	1992b	Decision analysis
Demicheli	1992	"Brown's exponential smoothing" forecasting technique
Bloom	1993	Decision analysis
Krahn	1993	Decision analysis + Markov chain analysis
Oddone	1993	Decision analysis
Eelkman Rooda	1994	Markov chain analysis
Margolis	1995	Decision analysis
Antoñanzas	1995	Markov chain analysis + "Compartmental dynamic model"
Kerleau	1995	Simple calculations of averted infections over 5 year period
Fenn	1996	Markov chain analysis with accommodation for "herd immunity effect" by means of changing transition probabilities
Beutels	1996	Decision analysis
Garuz	1997	Mathematical model based on differential equations, Markov chain analysis + Monte Carlo simulation
Wiebe	1997	Decision analysis + Markov chain analysis
Krahn	1998	Markov chain analysis

It appears from table 6 that decision analysis is the modelling technique that is used most often. Most studies that used this technique applied the cyclic algorithm designed by Mulley et al. [Mulley, 1982] and adapted it to fit the needs of the specific study. However, in recent years, more complex techniques such as Markov chain analysis and more mathematically oriented modelling techniques have been applied more often. Only few studies tried to accommodate for indirect immunisation effects, the so-called "herd immunity" effect (the reduction of infections over time due to the smaller stock of chronic carriers as the vaccination program proceeds over time). The use of static modelling techniques for the estimation of the effects of vaccination programs in general leads to overestimation of the benefits of these programs.

4.2.6 Duration of vaccination programs and time horizon for calculation of costs and effects

Table 7 shows the differences between selected studies in duration of vaccination programs on the one hand and the number of years for which the effects and costs of these programs were calculated on the other hand.

Table 7: Duration of health care intervention and time horizon used to calculate effects and costs

First author	Year of publication	Duration of vaccination program	Time period effects	Time period costs
Mulley	1982	1 year	1 year	20 years
Ginsberg	1992a	45 years	110 years	110 years
Ginsberg	1992b	36 years	70 years	70 years
Demicheli	1992	99 years	99 years	129 years
Bloom	1993	1 year	30 years	60 years
Krahn	1993	1 year	life-time	life-time
Oddone	1993	1 cohort of dialysis patients	3 years	10-30 years
Eelkman Rooda	1994	100 years	100 years	100 years
Margolis	1995	1 year	45 years	45 years
Antoñanzas	1995	12 years	22-32 years	22-32 years
Kerleau	1995	5 years	5 years	25 years
Fenn	1996	1-25 years	110 years	110 years
Beutels	1996	1 year	35 years	70 years
Garuz	1997	1 year	10-30 years	10-30 years
Wiebe	1997	1 year	life-time	life-time
Krahn	1998	1 year	life-time	life-time

Table 7 shows that the different studies have used quite different time periods for both the vaccination program itself and the calculation of the effects and costs over time. The duration of the program varied between 1 and 100 years. The time horizon for the calculation of the effects of programs varied between 1 and 110 years. The maximum time horizon for the calculation of costs was even longer, at 129 years.

4.2.7 Costs of vaccine

Table 8 provides with information on the parameters that were used for the costs of vaccine (for a complete cycle of 3 vaccinations), the source that was mentioned for the costs of the vaccine and the year of costing that was used for all cost data in the study.

Table 8: Costs of vaccine (currency), source that was used for vaccine costs and base year for all other costing

First author	Year of publication	Costs of vaccine and currency	Source	Base year for costing data
Mulley	1982	US$ 100 [a]	Charges	1980
Ginsberg	1992a	US$ 6.19	Manufacturer	1990
Ginsberg	1992b	US$ 6.57	Manufacturer	1990
Demicheli	1992	US$ 10	Literature	Not given
Bloom	1993	US$ 160 (new-borns) US$ 225 (adolescents)	Hospital pharmacy	1989
Krahn	1993	Can$ 39.30	Not given	1990
Oddone	1993	US$ 114	Hospital pharmacy	1987
Eelkman Rooda	1994	[b]	[b]	1991
Margolis	1995	US$ 20 (new-borns) US$ 40 (adolescents)	"Federal contract price"	1993
Antoñanzas	1995	PTA 2400 (new-borns) PTA 3900 (adolescents)	Manufacturer	1992
Kerleau	1995	FF 420	Charges	1991
Fenn	1996	£ 26	Not given	1992/1993
Beutels	1996	BEF 1200	Manufacturer	1995
Garuz	1997	US$ 21.2 (new-borns) US$ 28.4 (adolescents)	Manufacturer	1993
Wiebe	1997	Can$ 14 (new-borns) Can$ 28 (adolescents)	Not given	1993
Krahn	1998	US$ 20	Ministry of Health contract price	1994

[a] including fees for handling and administration

[b] the cost of vaccine was not included in the Base Case Scenario, because study was set up as a threshold analysis (at what vaccine price can a vaccination campaign be organised in a cost-neutral way?)

Table 8 shows that large differences in the assumptions on the costs of vaccine appear within the selected studies. The lowest vaccine costs that were found were as low as US $ 6 (1989 cost data) for a complete cycle, the highest costs ranged to US $ 160 per cycle of 3 doses (1990 cost data).

4.2.8 Different cost data included in studies

Three major types of cost data may be distinguished in economic evaluations: direct, indirect and intangible costs. Direct costs consist of both the costs for the vaccination program and the costs for the treatment of hepatitis B and its long-term sequelae (e.g. acute hepatitis, cirrhosis, and hepatocellular carcinoma). Indirect costs are generated by productivity loss due to morbidity or premature mortality. Intangible costs are the costs associated with suffering and pain due to ill health, and, in case of premature death, the value of human life itself. Table 9 provides with information on the different cost categories that were included in the selected studies.

Table 9: Different types of cost data included in the selected studies

First author	Year of publication	Direct costs	Indirect costs	Intangible costs
Mulley	1982	yes	no	no
Ginsberg	1992a	yes	yes	no
Ginsberg	1992b	yes	yes	no
Demicheli	1992	yes	yes	yes
Bloom	1993	yes	no	no
Krahn	1993	yes	yes	no
Oddone	1993	yes	no	no
Eelkman Rooda	1994	yes	yes	no
Margolis	1995	yes	yes	no
Antoñanzas	1995	yes	no	no
Kerleau	1995	yes	no	no
Fenn	1996	yes	no	no
Beutels	1996	yes	yes	no
Garuz	1997	yes	no	no
Wiebe	1997	yes	no	no
Krahn	1998	yes	yes	no

Not surprisingly, all studies incorporated direct medical costs. Indirect costs were considered in 50 percent of the selected studies. Only one study attempted to calculate intangible costs. About half of the studies reported an in-depth study of direct medical costs. Such in-depth cost studies consist for instance of reviews of patient charts to gain insight in levels of medical consumption in different stages of disease, expert panels on the most likely course of a chronic hepatitis B infection, and detailed studies on actual costs of health care, not charges. The other half of the studies either quoted data from the more sophisticated studies, or simply made estimates and assumptions from the literature or consulted one or two experts. Those studies that included indirect costs all made assumptions on the number of working days lost due to hepatitis B.

4.2.9 Discounting

Because any intervention directed at the prevention of hepatitis B infections requires that investments have to be made at present, while benefits of this investment are also realised in the distinct future, it is essential that a correction for these differences in time perspective is made. Health economists do agree on the fact that future costs need to be discounted, that means expressed in today's currency. Therefore, future costs weigh less heavily than today's costs. The annual discount rate may differ between countries and is also time-pendent. Relevant recommendations for this rate are:

- 3% (Panel on Cost-Effectiveness in Health and Medicine [Gold, 1996])
- 4% (Dutch Guidelines for Pharmaco-Economic Research [CVZ, 1999] and Dutch Ministry of Finance [Ministry of Finance, 1996])
- 5% (Canadian Guidelines for Economic Evaluation of Pharmaceuticals [CCOHTA, 1997])

However, there is ongoing controversy among health-economists on the necessity to discount future benefits as well. [van Hout, 1998] Table 10 shows the policies that selected studies have chosen with regard to discounting of future costs and benefits, and the discount rate that was used in the Base Case calculations.

Table 10: Discounting of future costs and benefits and discount rate used

First author	Year of publication	Discounting of costs	Discounting of benefits	Discount rate
Mulley	1982	yes	no	6 %
Ginsberg	1992a	yes	no	7.5 %
Ginsberg	1992b	yes	no	7.5 %
Demicheli	1992	yes	no	8 %
Bloom	1993	yes	no/yes	5 %
Krahn	1993	yes	yes	5 %
Oddone	1993	yes	no	5 %
Eelkman Rooda	1994	no [a]	no [a]	0 % [a]
Margolis	1995	yes	no/yes	5 %
Antoñanzas	1995	yes	no/yes	5 %
Kerleau	1995	yes	no	8 %
Fenn	1996	yes	no/yes	6 %
Beutels	1996	yes	no/yes	5 %
Garuz	1997	yes	no/yes	5 %
Wiebe	1997	yes	yes	5 %
Krahn	1998	yes	no/yes	3 %

[a] Baseline results presented undiscounted, but 5 and 10 % discount rates applied in sensitivity analyses

It appears from table 10 that only one study chose to present undiscounted cost data. Discount rates varied between 3 and 8 percent in the baseline calculations of results. By the choice of a more conservative (lower) discount rate, more weight is attached to future costs and benefits than by the choice of a higher discount rate. About half of the studies resolved the controversy on the necessity to discount future benefits by presenting both discounted and undiscounted data on the benefits of the vaccination program. Almost all studies evaluated the influence of the choice for a specific discount rate in sensitivity analyses (see further).

4.2.10 Sensitivity analysis

One of the elements of a good economic evaluation is that the influence of the assumptions made and the parameter values chosen are subjected to a sensitivity analysis. The aim of a sensitivity analysis is to study whether conclusions that are drawn in the baseline analysis would change if other baseline parameter values were chosen. Table 11 shows which parameters were subjected to sensitivity analyses in the different studies, and which parameters appeared to be most influential for the final results of the study.

Table 11: Variables included in the sensitivity analyses and most influential variables

First author	Year of publication	Variables included	Most influential variables
Mulley	1982	Costs of HBV infection, Vaccine efficacy, Vaccination costs, Natural history of HBV infection, HBV incidence in target population, The inclusion of indirect costs	Screening costs, Vaccination costs, Costs of HBV infection, HBV incidence, The inclusion of indirect costs
Ginsberg	1992a	Discount rate, Vaccine effectiveness decay, Degree of underreporting of acute hepatitis B cases, The inclusion of indirect costs	Discount rate, The inclusion of indirect costs
Ginsberg	1992b	Discount rate, Vaccine effectiveness decay, Degree of underreporting of acute hepatitis B cases, Compliance with vaccination, Vaccination costs, The inclusion of indirect costs	Vaccination costs, Discount rate, The inclusion of indirect costs
Demicheli	1992	HBV incidence, Discount rate, Costs of HBV infection, The inclusion of indirect and intangible costs	HBV incidence, Discount rate, Costs of HBV infection, The inclusion of indirect and intangible costs
Bloom	1993	Vaccination costs, Vaccine efficacy, Natural history of HBV infection, Discounting of non-monetary benefits	Vaccination costs, Discounting of non-monetary benefits
Krahn	1993	Vaccination costs, Discount rate, Prevalence of carrier state, HBV incidence, Percentage of infections progressing to chronic stage, Natural history of HBV infection, Duration of vaccine efficacy, Compliance with vaccination, Costs of HBV infection	Vaccination costs, Discount rate, Percentage of infections progressing to chronic stage, HBV incidence, Du-ration of vaccine efficacy
Oddone	1993	Vaccine efficacy, Costs of HBV infection, Vaccination costs, HBV incidence	Vaccination costs, HBV incidence, Vaccine efficacy
Eelkman Rooda	1994	HBV incidence, Natural history of HBV infection, Inclusion of costs of screening blood donors, Costs of HBV infection, Vaccine efficacy, Discount rate, The inclusion of indirect costs	Inclusion of costs of screening blood donors, Discount rate, The inclusion of indirect costs
Margolis	1995	Vaccination costs, Compliance with vaccination, Costs of HBV infection, Discount rate, The inclusion of indirect costs, Percentage of infections progressing to chronic stage, Natural history of HBV infection, Prevalence of	Discount rate, Vaccination costs, Prevalence of HBV infection (estimated life-time risk of infection), (influence of other variables not reported)

First author	Year of publication	Variables included	Most influential variables
		HBV infection (estimated life-time risk of infection)	
Antoñanzas	1995	Transplant probability, Years of follow-up, Cirrhosis costs, Compliance with vaccination, Vaccination costs, Discount rate, Costs of HBV infection, Percentage of infections progressing to chronic stage, HBV incidence	Vaccination costs, Discount rate, Percentage of infections progressing to chronic stage, HBV incidence, Discount rate
Kerleau	1995	Discount rate, Compliance with vaccination, Vaccination costs, Costs of HBV infection, HBV incidence	HBV incidence, Vaccination costs
Fenn	1996	HBV incidence, Degree of underreporting of acute hepatitis B cases, Percentage of infections progressing to chronic stage, Risk of cirrhosis, Risk of HCC, Costs of HBV infection, Organisational costs, Discounting of non-monetary benefits	Discounting of non-monetary benefits, HBV incidence, Degree of underreporting of acute hepatitis B cases, Percentage of infections progressing to chronic stage, Risk of cirrhosis
Beutels	1996	Discount rate, Natural history of HBV infection, The inclusion of indirect costs, Vaccination costs	Discount rate, The inclusion of indirect costs, Vaccination costs
Garuz	1997	Costs of HBV infection, Discount rate, Vaccination costs, Epidemiological assumptions (not specified), Time horizon for calculation of effectiveness, Increase of indirect costs	Vaccination costs, Time horizon for calculation of effectiveness
Wiebe	1997	Discount rate, Vaccine effectiveness decay, HBV incidence, Vaccination costs, Costs of HBV infection, Compliance with vaccination, Natural history of HBV infection	Discount rate, Vaccine effectiveness decay, HBV incidence, Vaccination costs
Krahn	1998	HBV incidence, Vaccination costs, Degree of underreporting of acute hepatitis B cases, Percentage of infections progressing to chronic stage, Discount rate, Vaccination costs, Duration of vaccine efficacy, Costs of HBV infection	HBV incidence, Vaccination costs (influence of other variables not reported)

In reporting the results of sensitivity analyses, not all studies have applied similar reporting standards. Therefore, it was sometimes difficult to assess the outcomes of sensitivity analyses. Some authors have used relative changes towards the baseline estimates as a measure of robustness of results. In these cases, it was relatively easy to assess and control the results of

sensitivity analyses. However, other studies have used some arbitrary threshold of cost-effectiveness, such as cost per life year gained not exceeding US $ 50.000. As long as changing baseline assumptions did not result in cost-effectiveness ratios above this arbitrary threshold, it was concluded that outcomes were insensitive to changes in baseline assumptions. Such conclusions are much more difficult to control for readers of these papers. The data in the last column of Table 11 should therefore not be regarded as an exhaustive overview of all sensitive parameters, but merely as a minimum set of parameters that appear important for the determination of the robustness of the models used. The following parameters were most often shown to have a significant impact on the results of a study:

1. Vaccination costs
2. Discount rate
3. HBV incidence
4. The inclusion of indirect costs/benefits
5. The percentage of infections progressing to chronic stages of disease
6. Discounting of non-monetary benefits
7. Costs of HBV infection, including long-term consequences such as cirrhosis and liver cancer

It is also possible to create a shortlist of parameters that in general seem to have a rather limited influence on the cost-effectiveness of HBV vaccination programmes:

- The natural history of chronic HBV infection (the percentage of patients that will develop long-term sequelae of HBV infection). This excludes the percentage of patients progressing to the chronic stage of disease, as mentioned above.
- Factors associated with vaccine effectiveness: the efficacy of the vaccine, compliance with vaccination, the duration of vaccine efficacy, and the decay in vaccine efficacy over time.

4.2.11 Conclusions reached on economic attractiveness of evaluated programs

The cost-effectiveness and cost-benefit ratios that were reported in the 16 papers are shown in Table 12. These ratios refer to the baseline outcomes of studies. If possible, the range in outcomes is provided as well.

Table 12: Cost-effectiveness and cost-benefit ratios (with ranges) as reported in baseline outcomes of selected studies (per program evaluated)

First author	Year of publication	Cost-effectiveness ratio	Benefit-cost ratio	Ranges	• Remarks and conclusions
Mulley	1982	Cost per case prevented: US$ 10.000 (attack rate 0.3 %) US$ 2.000 (attack rate 1 %) US$ 0 (attack rate 5 %)	Benefit-cost ratio > 1 in populations with annual attack rates above 5 %	-	• Imprecise data because abstracted from figure • annual attack rate in general population = 0.1 % • General vaccination is probably cost saving in I.V. drug users and homosexual men
Ginsberg	1992a	-	Benefit-cost ratios of neonatal vaccination program: 1.56 (direct cost only) 2.80 (direct and indirect cost)	In sensitivity analyses: 0.68-21.31 (direct costs only) 1.23-27.01 (direct + indirect costs)	• Benefit to cost ratio only < 1 if discount rate of 10 % used • Neonatal vaccination strategy is cost saving for both health care system and society
Ginsberg	1992b	-	Benefit-cost ratios of under-16-year-olds vaccination program: 1.88 (direct cost only) 3.57 (direct and indirect cost)	In sensitivity analyses: 0.80-42.10 (direct costs only) 1.48-122.97 (direct + indirect costs)	• Benefit to cost ratio only < 1 if discount rate of 10 % used • Under-16-year-olds vaccination strategy is cost saving for both health care system and society
Demicheli	1992	-	Benefit-cost ratio of neonatal vaccination program always < 1 in basecase	Benefit-cost ratio >1 if high future costs of HBV infection were assumed (US$ 17 million! per case)	• With epidemiological pattern of declining incidence of HBV infections, general vaccination will most likely never be an efficient strategy

First author	Year of publication	Cost-effectiveness ratio	Benefit-cost ratio	Ranges	• Remarks and conclusions
Bloom	1993	Cost per life-year saved: US$ 375-3.695 (mixed childhood strategy) US$ 3.066-38.632 (newborns) US$ 13.938-97.256 (adolescents) US$ 54.524-257.418 (adults)			• lower limit referring to undiscounted benefits, higher limit referring to discounted benefits • Universal vaccination of newborns is cost-saving at vaccine price below US$ 34 • Mixed childhood vaccination strategy is most cost-effective
Krahn	1993	Cost per life-year saved: (newborn strategy in comparison with selective strategy): US$ 30.347 (societal perspective) US$ 57.197 (third party payer perspective)		From a societal perspective: dominant (both lower cost and longer life-expectancy) to US$ 214.000 From 3rd party-payer perspective: US$ 11.000-US$ 253.000	• Cost-effectiveness ratios all refer to discounted benefits • Vaccination of newborns is cost-saving at vaccine price below US$ 7
Oddone	1993	Cost per life-year saved: US$ 583.333 (predialysis) US$ 493.902 (dialysis patients)		Cost per life-year saved < US$ 50.000 at annual attack rates > 2 %	• Cost-effectiveness ratios all refer to undiscounted benefits • local incidence rates important to choose strategy
Eelkman Rooda	1994	*Study results not reported in standard way*			• Vaccination of newborns + catch-up strategy is cost-saving at vaccination price of NLG 68 (5 % discounted costs)

First author	Year of publication	Cost-effectiveness ratio	Benefit-cost ratio	Ranges	• Remarks and conclusions
Margolis	1995	Cost per life-year saved: US$ 1.522-20.619 (infant immunization) US$ 3.730-27.919 (adolescent immunization)		Cost per life-year saved in worst-case scenario: US$ 6.097-68.528 (infants) US$ 15.019-90.503 (adolescents)	• lower limit referring to undiscounted benefits, higher limit referring to discounted benefits
Antoñanzas	1995	Cost per case prevented after 10 years: PTA 158.000-254.000 (infants) PTA 49.000-82.000 (adolescents) PTA 79.000-129.000 (combined)		Cost per case prevented after 10 years: PTA 114.000-183.000 (infants) PTA 39.000-61.000 (adolescents) PTA 61.000-97.000 (combined)	• lower limit referring to undiscounted benefits, higher limit referring to discounted benefits • Results more favorable with 20 year time horizon • Mass adolescent vaccination is most cost-effective
Kerleau	1995	Cost per case prevented: FF 160.000 (general population) FF 36.513 (young males) FF 3.613 (homosexuals) FF –5.935 (I.V. drug users)		FF 65.000-159.000 (general population) FF 3.429-35.329 (young males) FF –13.021-2.429 (homosexuals) FF –17.795-–7.119 (I.V. drug users)	• Vaccination programs directed at I.V. drug users are cost-saving • programs directed at homosexuals could be cost-saving depending on assumptions made • Cost-effectiveness ratios all refer to undiscounted benefits

First author	Year of publication	Cost-effectiveness ratio	Benefit-cost ratio	Ranges	• Remarks and conclusions
Fenn	1996	Cost per life year gained: £ 5.234-227.130 (infants) £ 9.646-301.365 (children) £ 8.470-233.379 (adolescents) £ 6.827-231.115 (combined)		Cost per life year gained of infant program: £ 954-12.944 (undiscounted benefits) – £ 72.474-502.569 (discounted benefits)	• lower limit referring to undiscounted benefits, higher limit referring to discounted benefits • programs of longer duration are less cost-effective than shorter programs • vaccination of infants is most cost-effective strategy
Beutels	1996	Cost per life year gained: BEF 2.947-21.260 (infants) BEF 3.299-17.628 (adolescents) BEF 3.077-19.633 (catch-up)	Benefit-cost ratios: Infant program: 0.89 (direct cost only) 8.66 (direct and indirect cost) Adolescents program: 0.93 (direct cost only) 7.30 (direct and indirect cost) Catch-up strategy: 0.91 (direct cost only) 7.99 (direct and indirect cost)		• lower limit referring to undiscounted benefits, higher limit referring to discounted benefits • Vaccination is cost-saving (for health services system) at vaccine price below BEF 401 (newborns) and BEF 463 (adolescents)
Garuz	1997	Cost per case prevented: US$ 1.875 – 2.564 (infants) US$ 603 – 850 (adolescents) US$ 834 – 1.170 (combined) US$ 590 – 820 (adolescents + screening pregnant women)		Cost per case prevented (undiscounted): US$ 1.467 – 1.921 (infants) US$ 428 – 646 (adolescents) US$ 617 – 878 (combined)	• lower limit referring to undiscounted benefits, higher limit referring to discounted benefits • Results more favorable with 20 and 30 year time horizon • adolescents program + screening pregnant women most cost-effective

First author	Year of publication	Cost-effectiveness ratio	Benefit-cost ratio	Ranges	• Remarks and conclusions
Wiebe	1997	Cost per life-year saved: CAN$ 15.900 (infant immunization) CAN$ 97.600 (10-year-olds) CAN$ 184.800 (12-year-olds)		Cost per life-year saved: Dominant - CAN$ 60.400 (infant immunization) Dominant - CAN$ 309.800 (10-year-olds) CAN$ 6.300 – 722.600 (12-year-olds)	• Cost-effectiveness ratios all refer to discounted benefits • infant program consistently most cost-effective program
Krahn	1998	Cost per life-year saved for Canadian program: US$ 2.145 (school-based program – direct cost only) dominant strategy (school-based program – direct and indirect cost) Cost per life-year saved for US program: US$ 26.000 (school-based program – direct cost only)		Cost per life-year saved: dominant strategy – US$ 90.000	• Cost-effectiveness ratios all refer to discounted benefits

Table 12 shows that, despite careful selection of high quality studies, unequivocal conclusions on economic attractiveness of programs were not reached. Four studies have reported the cost per case prevented, five studies reported benefit-cost ratios and eight studies reported the cost per life year gained. However, some studies reported baseline data with discounted benefits and others did not. This makes direct comparison of study results very difficult.

Two studies considered programs directed at intravenous drug users and homosexual men (Mulley, 1980; Kerleau, 1995). They both concluded that such programs are possibly cost-saving. The two studies by Ginsberg et al. (Ginsberg, 1992a; Ginsberg, 1992b) both reported favourable benefit-cost ratios of neonatal and adolescent vaccination programs, but these studies were carried out in a country of intermediate endemicity. With respect to the study by Demicheli and Jefferson, it is difficult to see why such negative benefit-cost ratios were reported. The study used extreme high estimates of life-time costs of HBV infection (US$ 2.3 million) and relatively low vaccination costs (US$ 10), but still concludes that general vaccination campaigns in Italy probably never can be executed in an efficient way. This conclusion is contradictory to that reached in the Belgium study of Beutels et al. (Beutels, 1996), using much lower estimates of lifetime costs of HBV infection and higher vaccination costs. Beutels and colleagues concluded that general vaccination campaigns have benefit-cost ratios close to 1 when direct costs only were considered, and much higher than 1 if indirect costs and benefits were also estimated. In other words, the campaigns would lead to savings.

Those studies that have compared two or more programs reached different conclusions on the most cost-effective program. Three studies concluded that infant vaccination was most cost-effective (Wiebe, 1997; Fenn, 1996; Margolis, 1995), two studies considered programs directed at adolescents as most cost-effective (Antonanzas, 1995; Garuz, 1997) and one study concluded that a mixed strategy, directed both at newborns and 10-year-olds, was most cost-effective. Hence, the study outcomes significantly diverge and no general conclusion can be drawn.

5. General observations and discussion

The scientific discipline of health economics has developed considerably over the last 20 years. One reason for the fact that only 16 studies were selected out of hundreds of economically oriented studies on hepatitis B prevention is that methodological standards of the 1990s were used to assess studies from previous decades. But even recently published studies often fail to meet the basic methods of conducting and reporting economic evaluations, as has been extensively discussed in reviews by Jefferson and Demicheli. [Jefferson, 1994; Demicheli, 1997] In their 1994 review, applying quality criteria that more or less resemble ours (Appendix 2), only 10 good quality studies could be identified. As these authors did not provide with a list of these 10 studies, it is not possible to assess whether we have selected at least the same basic set of good quality studies. However, our conclusion that only few studies of excellent quality have been published is not at odds with the conclusions reached in earlier reviews.

One other reason for the fact that only 16 studies were selected is compromised in our application of very strict selection criteria. For instance, at least one general vaccination strategy had to be studied in the paper to merit selection. Some high quality studies that were directed at the cost-effectiveness of prenatal screening and subsequent immunisation of new-borns of infected mothers have consequently not been selected. So, our final selection is not a selection of all high quality economic evaluations of Hepatitis B prevention strategies, but of high quality economic evaluations of general vaccination strategies.

The two reviews of Jefferson and Demicheli were designed to avoid the introduction of possible publication bias. The authors wrote to each of the first or corresponding authors of the studies in their review, asking them to identify any further published or unpublished works on the subject of the economics of Hepatitis B vaccination. They concluded that there did not appear to be any differences in the key variables between published and unpublished studies. In their experience, there is little evidence for the existence of publication bias, the fact that studies reporting positive or impressive results are more likely to be published, in the field of hepatitis B economics. Considering the labour-intensity of such work, we therefore decided not to attempt to identify further unpublished studies.

One other finding of Jefferson and Demicheli, namely that a literature review based on MEDLINE searches alone does not yield all relevant studies, led us to use the extensive search strategy as described in paragraph 3.2.1. Indeed, 5 of the 16 studies that were ultimately selected for our review (31 %) could not be found in MEDLINE. One reason may be that some economic studies are not indexed with recognisable economic key-words. Another reason is simply that not all major journals are indexed in MEDLINE. For instance, *Vaccine*, an

important journal in the immunisation field that regularly publishes economically oriented papers, can not be found in MEDLINE.

In a recent overview of economic evaluation studies about hepatitis B vaccination, Beutels [Beutels, 1998] concluded that the cost-effectiveness ratio of universal HBV vaccination in low endemic countries resembles those of other prevention strategies such as universal measles vaccination, breast cancer screening and universal *Varicella* vaccination. However, Beutels only presented the results of 2 studies conducted in low endemic countries. In our review, the range of reported cost-effectiveness ratios for studies conducted in low endemicity areas is very wide and spans from savings [Beutels, 1996] to US$ 250,000 [Bloom, 1993] per life year saved. Based on these outcomes it seems not appropriate to speak about the cost-effectiveness ratios for HBV vaccination in general, as the variance of the cost-effectiveness ratios is so big. Thus, Beutels conclusion is not supported by our results.

The present investigation revealed important differences in methodology and in the definition and measurement of parameters. Many of these differences seem arbitrary and more a matter of convenience (accessibility of data and previous literature) than of a well-founded choice. However, many of the arbitrary choices made in the selected studies reflect the fact that uncertainty over the “real-life” value of important parameters exists, or the fact that parameter values may be completely different within different study settings. Economic evaluation studies in general are aimed at supporting local decision-makers. It certainly is not possible to transfer study results reached in one setting directly to another setting. In this respect, diversity within the selected studies should not be regarded as negative alone. However, the conclusions reached in the different studies have little practical relevance for policy-making in the Netherlands.

Within the general framework of accepted economic evaluation methodology, each new study should be adapted to local circumstances as good as possible. This was not always the case in the 16 selected studies, since important parameter values often simply have been copied from earlier publications, with completely different study settings. It is therefore difficult not to be worried over the relative ease with which study outcomes in this field may be “directed” with the choice of parameter values. One way to prevent such misuse of economic evaluation is the requirement of a sound and extensive sensitivity analysis. On the basis of such an analysis, it is possible to estimate the effect of chosen parameter values and the robustness of the model used. This literature review identified important parameters that usually have a significant impact on the results of economic studies about HBV vaccination. These parameters are vaccine costs, discount rate, hepatitis B incidence, exclusion of indirect costs and effects, not discounting of effects, the percentage of patients progressing to chronic stages of disease and the assumed life long costs of HBV infection (including long-term consequences such as cirrhosis and liver cancer). Thus, these variables should be subject of an extensive sensitivity analysis in any future study about this topic. However, the analysis should not be restricted to these parameters alone. Depending on

the study frame and setting, additional parameters may play an important role for the outcomes.

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List of abbreviations

AB	Abstract
Anti-HBe	Antibody against Hepatitis B e antigen
AU	Author
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CUA	Cost-Utility Analysis
DARE	Datavase of Reviews of Effectiveness
HAV	Hepatitis A Virus
HBcAg	Hepatitis B core Antigen
HBeAg	Hepatitis e Antigen
HBIG	Hepatitis B Immune Globulin
HbsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HEED	Health Economic Evaluation Database
IgM	Immunoglobulin M
INAHTA	International Network of Agencies of Health Technology Assessment
NEED	NHS Economic Evaluation Database
NHS	National Health Service
QALY	Quality Adjusted Life Year
SO	Source
TI	Title

Appendix 1 Mailing list

1	Hoofdinspecteur voor de Gezondheidszorg (plaatsvervanger), drs. P.H. Vree
2-3	Directeur-Generaal van de Volksgezondheid, prof. H.J. Schneider
4-5	Inspecteur Infectieziekten van de Inspectie Gezondheidszorg, J.K. van Wijngaarden, arts
6	Voorzitter van de Gezondheidsraad, prof. J.J. Sixma
7	Secretaris Werkgroep RVP, Gezondheidsraad, J. Sekhuis, arts
8	Ministerie van VWS, mw. drs. M. Esveld
9	Landelijke Vereniging van GGD's
10	Landelijke Coördinatiestructuur Infectieziektenbestrijding, drs. J.E. van Steenbergen
11	Nederlandse Hepatitis Stichting
12	Landelijk Infocentrum Hepatitis
13	Stichting AIDS Fonds
14	Stichting SOA-bestrijding
15	Bestuur Nederlandse Vereniging voor Studie van SOA
16	WHO, Global Programme for Vaccines and Immunisation, dr. M.A. Kane
17	WHO, European Regional Office
18	Instituut voor Medische Technology Assessment, Erasmus Universiteit Rotterdam, prof. F.F.H. Rutten
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48	Groningen University Institute for Drug Evaluation, drs. J. Bos
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52	prof. S.W. Schalm
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72	dr. L.J.M. Smits
73	drs. M.I. Dijkman
74	drs. L. Wijgergangs
75-90	medewerkers CZO
91-92	Auteurs
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94	Bureau Rapportenregistratie
95	Bibliotheek RIVM
96-110	Bureau Rapportenbeheer
111-125	Reserve exemplaren

Appendix 2 Checklist to evaluate economic studies

Nr	Items	4	3	2	1	0	N/A
1	Definition of study aim: Does a well-defined question exist? Are the perspective and alternatives compared clearly specified?						
2	Sample selection: Are the types of patients chosen suitable and are they specified? Are the diagnostic criteria adequately specified?						
3	Analysis of alternatives: Are all the relevant alternatives analyzed? Is / are the comparison alternative(s) suitable? Is this the most commonly used treatment, or one that will be replaced by the new drug? Is the indication the most relevant one? Are adequate doses used? Are the treatment reproducible (e.g. doses, interval, duration)? Is the "do nothing" option analyzed or should it be analyzed? Is a decision analysis applied?						
4	Analysis of perspective: Is it clearly specified (e.g. society, patient, hospital)? Is it justified for the question asked?						
5	Measurement of benefits: Is it adequate for the question asked and the perspective? Are the data on the effectiveness of alternatives adequately established? Is the main assessment variable (endpoint) objective and relevant? Is the time fixed for the evaluation sufficient and is it specified? Are the results quantified by time?						
6	Measurement of costs: Is it adequate for the question asked and the perspective? Are the costs up to date and are the prices those of the market? Is an adjustment for future costs and benefits performed?						
7	Is this type of analysis suitable? Financial terms: cost/benefit "Physical units": cost-effectiveness						

Nr	Items	4	3	2	1	0	N/A
	Quality of life/utility: cost utility Equal benefits: cost minimization						
8	Analysis of results: If intermediate variables are used, are they representative of the end benefit? Is a marginal analysis performed? Are the costs and consequences of adverse effects analysed?						
9	Is the evaluation suitable if made within a clinical trial? Is the suitable methodology used? Are the statistical methods used adequate? Is an analysis according to “intention to treat” made? Are costs resulting from the trial, which differ from those in normal practice, taken into account?						
10	Are the assumptions and limitations of the study discussed? Is a sensitivity analysis performed? Do the assumptions have a bias? Is the execution of any important variable analyzed or justified? If intermediate endpoints are assumed, are limitations discussed?						
11	Are possible ethical problems discussed and identified?						
12	Conclusions: Are they justified? Can they be generalized? Can they be extrapolated to daily clinical practice?						
13	Overall impression of the quality of the paper?						

4 = correct
3 = acceptable
2 = doubtful
1 = not reported
0 = incorrect
N/A = not applicable

Appendix 3 Parameter estimate form

Author/journal/year:

Nr.	Question	Range found in literature	This study
1.	Percentage of symptomatically (acute) infected persons that is hospitalised?	10 – 25 %	
2.	Percentage acute fulminant patients progressing to livertransplantation?	0 – 50 %	
3.	Percentage of acutely infected adults (both symptomatic and non-symptomatic) proceeding to chronic stages of disease? (chronic carrier of HBV virus)	3.5 – 10 %	
4.	Percentage of chronic carriers with active viral replication?	55 – 75 %	
5.	Percentage of patients with active viral replication treated with interferon?	10 – 50 %	
6.	Percentage of patients treated with interferon that benefits from the treatment / is treated successfully (that is transformation to 'healthy' carrier stage)?	35 – 46 %	
7.	Annual chance of spontaneous remission to 'healthy' carrier stage in patients with active viral replication?	1 – 19 %	
8.	Annual chance of developing compensated cirrhosis in patients with active viral replication?	1 – 10 %	
9.	Annual chance of developing decompensated cirrhosis in patients with compensated cirrhosis?	1.5 – 6 %	
10.	Annual chance of developing HCC in patients with compensated cirrhosis?	1 – 2.5 %	
11.	Annual chance of developing HCC in patients with decompensated cirrhosis?	2.5 – 13 %	
12.	Annual chance of dying in patients with HCC?	50 – 80 %	
13.	Annual chance of livertransplantation in patients with decompensated cirrosis?	0 – 25 %	
14.	Annual chance of dying in patients with compensated cirrhosis?	3 – 8 %	
15.	Annual chance of dying in patients with decompensated cirrhosis?	5 – 39 %	

Appendix 4 Description of study characteristics

FACTOREN BETREFFENDE HET LAND VAN DE STUDIE
WELK LAND
PREVALENTIECIJFER IN LAND VAN STUDIE
INCIDENTIECIJFERS IN LAND VAN STUDIE
BEVOLKINGSOPBOUW IN DAT LAND:GROEN OF GRIJS?

ALGEMENE GEGEVENS OVER DE STUDIE
INDICATOR KWALITEIT VAN DE STUDIE
DOEL VAN DE STUDIE
PERSPECTIEF VAN DE STUDIE
TYPE STUDIE
FINANCIER

VARIABELEN BETREFFENDE HET VACCINATIEPROGRAMMA
WELKE STRATEGIE DOORGEREKEND
WAAROM GEKOZEN VOOR DEZE STRATEGIE
DUUR VAN VACCINATIEPROGRAMMA (IN JAREN)
PERCENTAGE EFFECTIEF GEVACCINEERD
PERCENTAGE VAN DOELPOPULATIE GEVACCINEERD
DUUR VAN IMMUNITEIT (IN JAREN)

EFFECTIVITEITS ASPECTEN
EPIDEMIOLOGISCH MODEL VOOR EFFECTIVITEIT
WAT IS DE BELANGRIJKSTE UITKOMSTMAAT?
WELKE UITKOMSTMATEN WORDEN VERDER MEEGENOMEN?
TIJDSPANNE VAN EFFECTIVITEITS BEREKENINGEN

KOSTEN ASPECTEN
BASISJAAR VOOR KOSTENBEREKENINGEN
WELK ANALYTISCH MODEL VOOR KOSTEN
WELKE KOSTENCATEGORIEEN IN ANALYSE
KOSTEN VAN VACCIN
WELKE BRON GEBRUIKT VOOR KOSTEN VACCIN
WELKE BRON VOOR OVERIGE KOSTENGEGEVENS
TIJDSPANNE VAN KOSTENBEREKENINGEN BEHANDELINGEN
DISCONTERINGSVOET
WELKE ELEMENTEN WERDEN GEDISCONTEERD

SENSITIVITEITSANALYSE

WELKE VARIABELEN IN SENSITIVITEITSANALYSE
WELKE VARIABELEN BLIJKEN INVLOEDRIJK IN ANALYSE

CONCLUSIES

KOSTEN-EFFECTIVITEITS-RATIO VAN BESTE ALTERNATIEF
MEEST KOSTEN-EFFECTIEVE STRATEGIE
BELANGRIJKSTE AANBEVELINGEN

Appendix 5 Short reviews of selected studies (in chronological order)

TI: Indications for use of hepatitis B vaccine, based on cost-effectiveness analysis.
AU: **Mulley-AG; Silverstein-MD; Dienstag-JL**
SO: N-Engl-J-Med. **1982** Sep 9; 307(11): 644-52
AB: The cost effectiveness of the following three strategies against hepatitis B were examined: (a) vaccinating all persons without screening or (b) first screening of all persons and subsequently vaccinating those without evidence of immunity or (c) neither screening nor vaccinating persons but passively immunising all persons with known exposure. Homosexual men, surgical residents, and the general population of the United States were chosen as study population. Decision analysis was employed to estimate the cost-effectiveness of the different scenarios using a time horizon of 20 years. For the baseline analysis only direct medical costs were considered. In the discussion a very rough estimate of the indirect costs was also presented. Intangible costs were omitted. Costs but not effects were discounted at 6%. The following strategies would minimise the direct medical costs the most: 1. Screening followed by vaccination of homosexual men. 2. Vaccination without prior screening of surgical residents. 3. Neither screening nor vaccination of the general population. In general, vaccination of susceptible persons will save direct costs for populations with annual attack rates greater than a threshold between 5 per cent and 6 per cent. These results are very sensitive to screening and vaccination costs, costs of HBV infection, HBV incidence and the inclusion of indirect costs.

TI: Cost-benefit analysis of a nationwide neonatal inoculation programme against hepatitis B in an area of intermediate endemicity.
AU: **Ginsberg-GM; Shouval-D**
SO: J-Epidemiol-Community-Health. **1992** Dec; 46(6): 587-94
AB: In this article a cost-effectiveness analysis of a nation-wide neonatal vaccination campaign against hepatitis B in Israel for the 1990-2034 period is presented. Israel is situated in an area of intermediate endemicity, where the majority of HBsAg carriers are anti-HBe positive. Morbidity, mortality, utilisation, and cost data from Israeli and international sources were used. Direct medical and indirect costs but not intangible costs were considered in the cost-effectiveness framework. The societal perspective and the human capital approach were employed. A decision analysis model was developed for the calculation of the cost-effectiveness. Costs but not effects (decrease of the hepatitis B prevalence) were discounted at 7.5%. As time horizon 65 years were chosen consisting of 45 years of vaccination and 20 years of effects. All costs are shown in 1990 US$. Different neonatal vaccination strategies were considered. Because of economical and ethical reasons a policy of immunising all Israeli neonates was selected as dominant strategy. It would require investments of US$ 13.8 million but would lead to savings of around US$ 21.5 million in direct medical costs, US$ 16.6 million in indirect morbidity costs, and $ 0.6 million in averted premature mortality costs. Hence, the programme would generate

net savings of US$ 7.7 or US$ 24.9, depending on the exclusion or inclusion of indirect costs. Furthermore, this strategy would reduce the number of cases of hepatitis B during the 1990-2035 period in the cohort from 359,000 to 166,000. Benefit-cost ratios but no cost-effectiveness ratios are presented. The results are very sensitive to the choice of discount rate and the exclusion of indirect costs. Some direct cost are based on US data from 1984-85. Hence, they are unlikely to be adequate estimates for Israeli costs.

TI: Cost-benefit analysis of a nationwide inoculation programme against viral hepatitis B in an area of intermediate endemicity.
AU: **Ginsberg-GM; Berger-S; Shouval-D**
SO: Bull-World-Health-Organ. **1992**; 70(6): 757-67
AB: Due to the large decrease in the cost of vaccines against hepatitis virus B the authors performed a re-examination of the cost-effectiveness of a nation-wide vaccination campaign strategies in Israel. Israel is situated in an area of intermediate endemicity, where the majority of HBsAg carriers are anti-HBe positive. As screening strategy a viral hepatitis B prevention programme (with no prior screening) was selected that is targeted at all under-16-year-olds in Israel in 1990 and only neonates in the period 1991-2034. Morbidity, mortality, utilisation, and cost data from Israeli and international sources were used. A decision analysis model was applied for the computation of the cost-effectiveness. Applying the incidence based approach the direct medical as well as indirect but not intangible costs were estimated from the societal perspective. Productivity losses were calculated with the human capital approach. Cost but not effects (decrease of the hepatitis B prevalence) were discounted at 7.5%. As time horizon 70 years were selected. All costs are shown in 1990 US dollars. Benefit-cost ratios but no cost-effectiveness ratios were calculated. The investigated screening program would reduce the number of cases of viral hepatitis B in the vaccinated cohort from 654,000 to 270,000 over the period 1990-2059 yielding net savings of US$ 32 million when considering only direct costs. Inclusion also of the indirect costs increases the net savings to US$ 117.1 million. Even when the savings arising from the reduction in hepatocellular carcinoma and liver transplants were excluded, the vaccination program still renders savings. Sensitivity analysis showed that the vaccination costs, the discount rate and the exclusion of indirect costs are the most influential variables. The costs that are associated with treating hepatitis B were taken from the study “Cost-benefit analysis of a nation-wide neonatal inoculation programme against hepatitis B in an area of intermediate endemicity” by Ginsberg-GM and Shouval-D 1992. Thus, some direct cost are based on US data from 1984-85 and are unlikely to be adequate estimates for Israeli costs.
TI: Cost-benefit analysis of the introduction of mass vaccination against hepatitis B in Italy.
AU: **Demicheli-V; Jefferson-TO**

SO: J-Public-Health-Med. **1992** Dec; 14(4): 367-75

AB: The aim of the study was to evaluate the costs and benefits of introducing mass vaccination against hepatitis B in Italy. In Italy, compulsory vaccination of all new-born babies was started in 1991. Age-specific incidence rates of the last 20 years were extrapolated (including a 25 % increase) to future birth cohorts. The number of cases which are potentially avoidable per year with mass vaccination were calculated for the next 30 years. A 30 year cost profile for a chronic case of HBV was calculated. Direct, indirect and intangible costs were included. The marginal costs of the vaccination campaign were estimated. Cost and benefits were compared for 99 years following the introduction of the vaccination, using an 8 per cent discount rate. Despite the fact that all parameters were chosen so that the benefit-cost ratio would be as positive as possible (100 % vaccine efficacy, low vaccine costs, high treatment costs, high number of work days lost, high numbers progressing to chronic stages of disease), results show a continuous unfavourable benefit-cost ratio. Sensitivity analysis showed that results were sensitive to incidence rates, cost estimates and to the discount rate used. It is concluded that with the Italian pattern of declining incidence of the disease, universal vaccination most likely will never be an efficient strategy.

TI: A cost-effectiveness analysis of hepatitis B vaccine in predialysis patients.
AU: **Oddone-EZ; Cowper-PA; Hamilton-JD; Feussner-JR**
SO: Health-Serv-Res. **1993** Apr; 28(1): 97-121
AB: The objective of this study was to assess the cost effectiveness of hepatitis B vaccination in pre-dialysis patients. Costs and effectiveness of HBV vaccination was modelled with a decision tree constructed to analyse three vaccination strategies for patients with renal insufficiency: vaccine given prior to dialysis, vaccine given at time of dialysis, and no vaccine. Costs were calculated from estimated rates of health services use and unit costs of resource use, as observed in one hospital. Costs but not effects were discounted at 5 %. Efficacy data were based on probability estimates from the medical literature and included vaccination response rates, anticipated hepatitis B virus (HBV) infection rates, and outcomes from HBV. The study takes account of secondary transmission of the virus to household contacts of dialysis patients. Sensitivity analyses were performed to assess the effect of varying important clinical and cost variables. The number of patients requiring vaccination per case of HBV prevented was higher for dialysis patients (625 vaccinees/case prevented) than for pre-dialysis patients (434 vaccinees/case prevented). The cost-effectiveness ratios were $25,313/case of HBV prevented for vaccination at the time of dialysis and $31,111 for the pre-dialysis vaccine. Compared to the no vaccination strategy, cost per life year gained were $ 583,333 for the pre-dialysis strategy and $ 493,902 for vaccination at the initiation of dialysis. Results were sensitive to the cost of the vaccine and the incidence of HBV infection in dialysis patients. For the pre-dialysis strategy to become cost saving, the price of the vaccine would have to decrease from $114 to $1.50, or the incidence of infection would have to increase from 0.6 percent to 38 percent, holding all other variables constant. The study demonstrates that additional HBV infection can be prevented by immunising pre-dialysis patients, but at a very high cost

and that decisions concerning vaccination policy should be influenced by local prevalence of HBV infection.

TI: Should Canada and the United States universally vaccinate infants against hepatitis B? A cost-effectiveness analysis.
AU: **Krahn-M; Detsky-AS**
SO: Med-Decis-Making. **1993** Jan-Mar; 13(1): 4-20
AB: This paper examines the economic attractiveness of universal vaccination of infants with hepatitis B virus (HBV) vaccine by calculating the incremental cost-effectiveness of this strategy when compared with the currently recommended strategy (in Canada and the United States) of screening all pregnant women and vaccinating only infants born to HBsAg+ mothers. A decision-analytic model involving a Markov process to model the long-term sequelae of HBV infection was constructed to estimate the expected costs and life expectancies for a cohort of newborns (1991) under two strategies: the current screening policy (SELECTIVE), which involves active and passive vaccination of infants born to carrier mothers, and a policy that combines the current screening strategy (including active and passive vaccination of infants born to carriers) with active vaccination alone for children of non-carriers (UNIVERSAL). Cost estimates were derived from hepatologists, review of hospital charts and National (Canadian) hospital utilisation data. In the base-case analysis, both costs and effects are discounted at a rate of 5 %. Two different perspectives were analysed: a societal perspective and a third-party-payer perspective. From a societal perspective, the incremental cost required to achieve one extra life year with the UNIVERSAL strategy was found to be $30,347, in comparison with $ 34,462 for the SELECTIVE strategy. The result is sensitive to the duration of vaccine effectiveness, the prevalence of carrier status in the population, the annual incidence of infection, the proportion of infected persons that progress to chronic infection, the discount rate and particularly to the price of the vaccine. Universal vaccination results in net cost saving at a vaccine price of approximately $7 per dose, from a societal perspective. It is concluded that universal vaccination against HBV in infancy is economically attractive. Lower vaccine prices would substantially improve the attractiveness of such a program. Implementation of universal vaccination should be considered in North America, contingent on vaccine price reduction. This is a very comprehensive study, performed according to high methodological standards. The study provides with an extensive appendix, in which the relevant details of epidemiological data and assumptions are described.

TI: A reappraisal of hepatitis B virus vaccination strategies using cost-effectiveness analysis.
AU: **Bloom-BS; Hillman-AL; Fendrick-AM; Schwartz-JS**
SO: Ann-Intern-Med. **1993** Feb 15; 118(4): 298-306
AB: This study aims to determine clinical and economic consequences of alternative vaccination strategies for preventing hepatitis B virus infection. Decision analysis was used to evaluate costs, outcomes (number of cases prevented, deaths prevented, years of life saved),

and cost-effectiveness of three HBV management strategies ("no vaccination," "universal vaccination," and "screen and vaccinate") in four populations (new-borns, 10-year-old adolescents, a high-risk adult population with annual infection rates of 5 %, and the general adult U.S. population of 12 to 50 years old). In addition, a combined strategy of screening pregnant women and vaccination of 10 year-old adolescents was examined. Each analysis followed a cohort of 10.000 individuals for three consecutive 10-year periods. Information on HBV incidence and prevalence, clinical course, and management of acute illness and chronic sequelae was obtained from the literature and a panel of experts. Actual payments (1989 costs) were obtained from Blue Cross/Blue Shield and local pharmacies. Only direct medical costs were taken into account. Costs were discounted at a 5 % discount rate, outcomes were presented both discounted and not discounted. Incremental cost-effectiveness was calculated from the perspective of the payer of medical care and subjected to sensitivity analysis. The sensitivity analysis comprised a worst-case scenario (relatively unfavourable towards vaccination) and a best-case scenario (relatively favourable towards vaccination). Vaccination (with or without screening) prevents more disease at somewhat increased cost than no vaccination for the neonatal, adolescent, and adult populations. Vaccination (with or without screening) is a dominant strategy in adult high-risk populations (lower cost and greater benefit than no vaccination). Of all strategies compared, optimal cost-effectiveness, with non-monetary benefits not discounted, results with the combined strategy of screening pregnant women, administration of HBIG and vaccine to new-borns of infected mothers, and vaccination of all children at age 10 and again 10 years later (incremental cost-per-year-of-life-saved relative to the "no vaccination" strategy is $375). A strategy of universal new-born vaccination alone leads to an incremental cost-per-year-of-life saved of $3332. If adolescents are vaccinated at age 10, incremental cost-per-year-of-life saved is $13,938; for the general adult population, the incremental cost-per-year-of-life saved of universal vaccination of adults is $54,524. Discounting benefits will increase cost-per-year-of-life saved 7 to 12 times for all strategies. The differences in cost per year of life saved between the best and worst-case scenario varied approximately twofold, and relative preferences of the strategies examined did not change.

TI: Vaccinatie tegen hepatitis B. Kosten en effecten van eradicatiestrategieën.

AU: **Eelkman Rooda HM, Barendregt JJM, van Hattum J, van Hout BA**.

SO: Erasmus Universiteit, iMTA rapport nr. 94.32, **1994**.

AB: The authors have developed a model (HEPAB) to estimate the costs and effects of 4 different scenario’s to prevent hepatitis B. The first scenario is the situation in which no specific preventive program is carried out and serves only as a reference scenario. A second scenario represents the current preventive strategy of screening of pregnant women and subsequent immunisation of new-borns of HBsAg infected mothers. The two last scenarios are scenarios aimed at eradication of hepatitis B. One scenario concerns the situation in which all new-borns are vaccinated. The second eradication scenario is the strategy in which for the next 10 years, in addition to all new-borns, all children at age 10 are also vaccinated. For each scenario, cumulative costs and effects are calculated for a period of 100 years, starting in

1990. HEPAB is organised as a Markov-chain model. The effectiveness of vaccination is assumed to be 100 percent, and to last a life-time. Costs per stage of disease were estimated on the basis of a survey of medical records combined with expert opinion. Costs of vaccination were ignored in the base-case calculations, facilitating a threshold analysis to determine the break-even point at which vaccination is cost-neutral (equal cumulative costs of vaccination scenario and screening only scenario). Indirect costs were estimated by experts and valued using the friction costs method. In the two eradication scenarios, it was assumed that screening of blood donors and pregnant women would continue for some years, but could be terminated eventually. The results are presented using a discount-rate of 0 %, but 5 % and 10 % discount rates have been used in a sensitivity analysis. Excluding the costs of the vaccination strategy, the combined vaccination scenario is a dominant strategy, resulting in less cumulative costs and more life years gained than any of the other strategies. The scenario in which children are vaccinated at age 0 and during 10 years at age 10, saves costs if the costs per course of vaccination do not exceed ƒ 136,-. When costs and effects are discounted at 5 % or 10 %, the same scenario generates savings only if costs per course of vaccination are below ƒ 68,- or ƒ 25,-, respectively. So, results are very sensitive to the discount rate used, the inclusion of indirect costs and to the assumed termination of screening after some years.

TI: Analyse coût-avantage d'une politique de prévention vaccinale de l'hépatite virale B [Cost-benefit analysis of vaccinal prevention of hepatitis B policy]

AU: **Kerleau-M; Flori-YA; Nalpas-B; Lanoe-JL; Berthelot-P; Fardeau-Gautier-M**

SO: Rev-Epidemiol-Sante-Publique **1995**; 43(1): 48-60

AB: Current French vaccination policies primarily aim at most exposed populations (patients under dialysis, hospital workers, infants born to VHB+ mothers). This article claims to be a cost-benefit analysis, but in fact it is a cost-effectiveness analysis. This article evaluates different strategies ("no vaccination", "universal vaccination" and "vaccination after screening") for four different populations with contrasted exposure (French general population, young men adults, homosexual men and intravenous drug users). The primary outcome measure is the number of infections prevented, the economic outcome measure is the net cost per case averted. All preventive programs are assumed to be implemented for a 5-year period, effectiveness is measured for the same period. Vaccination was assumed to be effective in 95 % of cases vaccinated. It is estimated that the incidence of hepatitis B is 1/1000. Effectiveness is modelled separately for the four target populations, based on group-specific estimates of annual attack rates. Life-time (= 20 years after infection) direct medical costs for a case of hepatitis B are estimated, based on protocols and retrospective medical record tracking. The total costs for vaccination are assumed to be FF 760 per person. Indirect cost and benefits were not considered. Costs were discounted at 8 %, effects were not discounted. The cost per case averted in general vaccination programs are FF 160.000 (general population), FF 36.513 (young males), FF 3.613 (homosexuals) and FF –5.935 (I.V. drug users). Compared to the status quo (no general vaccination), both preventive strategies (vaccinate all vs. screen + vaccinate) directed at intravenous drug users were cost-saving. Programs directed at homosexuals

may also be cost-saving, depending on the assumptions made. Results appear to be sensitive to the costs of vaccination and to the estimated life-time costs of HBV infection. Results are less sensitive to the discount rate applied and the compliance rate. Unfortunately, the assumptions on attack rates were not explored in the sensitivity analysis.

TI: Cost-effectiveness analysis of hepatitis B vaccination strategies in Catalonia, Spain.
AU: **Antonanzas F, Garuz R, Rovira J, Anton F, Trinxet C, Navas E, Salleras L.**
SO: PharmacoEconomics **1995**; 7(5): 428-443.
AB: This study is located in the province of Catalonia, Spain. Three different vaccination strategies were evaluated for its cost-effectiveness: (1) mass immunisation of 12-year old adolescents; (2) mass immunisation of infants; and (3) combined mass immunisation. Strategies were implemented for a 12-year period, but boosters were assumed to be given 10 years after vaccination. Markov models were used to estimate effectiveness and costs under the various strategies. It was assumed that the annual infection rate remains constant. Each strategy was evaluated either alone or in combination with a screening programme for HBV in all pregnant women and vaccinating and administering HBIG to infants at risk of contagion. Healthcare costs were measured in monetary units, and effectiveness in terms of cases of HBV infection avoided. Indirect and intangible costs were not included. Each vaccinated cohort was followed for 10 or 20 years to assess costs, benefits and effects stemming from vaccination. Future costs were discounted at a 5 % rate, and benefits were both presented discounted and not discounted. Almost all analyses showed that the mass adolescent vaccination was the most cost-effective strategy and the mass infant immunisation was the least efficient option. The cost per avoided HBV infection of the adolescent strategy ranged from PTA 2000 to PTA 82000. When any of these strategies is complement by screening for HBV in pregnant women, the number of avoided cases is always higher and the cost per avoided case decreases or remains unchanged. Sensitivity analysis revealed that the parameters most affecting final results were, in order of importance, the cost of the vaccine, the discount rate and chronic infection healthcare costs.

TI: Prevention of hepatitis B virus transmission by immunization. An economic analysis of current recommendations [see comments]
AU: **Margolis-HS; Coleman-PJ; Brown-RE; Mast-EE; Sheingold-SH; Arevalo-JA**
SO: JAMA. **1995** Oct 18; 274(15): 1201-8
AB: The cost-effectiveness of the following immunisation strategies was estimated. (a) screening of pregnant women and subsequent active and passive vaccination of infants born to HBsAg-positive mothers (b) routine infant vaccination, or (c) routine adolescent vaccination. The lifetime costs and effects of the different strategies were calculated for a cohort by employing decision analysis. Direct medical and indirect costs but no intangible costs were included. A discount rate of 5% and the human capital approach were used. Screening of pregnant women and subsequent active and passive vaccination of infants born to HBsAg-positive mothers prevents 5% of the acute and 29% of the chronic HBV infections that occur

during lifetime. Universal infant vaccination reduces the lifetime risk of HBV infection by 68%. Universal adolescent vaccination reduces the lifetime risk by 45%. From a societal perspective, each strategy was found to be cost saving, but was not cost saving with respect to direct medical costs. The average costs per undiscounted (discounted) life-year saved are US$ 164 (US$ 2701) for screening of pregnant women and subsequent active and passive vaccination of infants born to HBsAg-positive mothers, US$ 1522 (US$ 20619) for infant vaccination, and US$ 3730 (US$ 27919) for adolescent vaccination. These outcomes were shown to be very sensitive to the discount rate, the vaccination costs and the prevalence of HBV infection.

TI: Universal hepatitis B vaccination in Flanders: cost-effective? [Algemene vaccinatie tegen hepatitis B in Vlaanderen: kosten-effectief?]
AU: **Beutels P, Tormans G, van Damme P, van Doorslaer E.**
SO: Tijdschr Soc Gezondheidsz **1996**; 74: 272-281
AB: By means of a mathematical simulation model, an economic evaluation of universal vaccination against hepatitis B in Flanders, Belgium was performed. Epidemiological, clinical and economic data were gathered from published and unpublished sources and expert opinion. Incidence (annual “attack rate”) was modelled from prevalence data. Study results were presented both from a societal and from a payer perspective. The decision tree incorporated recent developments in the treatment of hepatitis B (interferon, liver transplant). Three universal vaccination strategies were compared to doing nothing: 1) vaccination of all infants; 2) vaccination of all 12-year olds; 3) combination of both strategies during eleven years. Effects on a closed cohort of 65000 new-borns were modelled. Cost-effectiveness ratios (only direct medical costs) are about BEF 1500 per infection prevented or BEF 3100 per discounted life-year gained for all three strategies. Vaccination of 12-year-olds is slightly more cost-effective for the health care payer, but is less cost-saving from society’s viewpoint than vaccination of infants. Neither strategy is dominant. Inclusion of indirect costs made the infant strategy somewhat more efficient than the other two strategies. The immediate intervention costs can be recovered entirely during the vaccinees’ lifetime if the costs of the vaccine per dose (including administering costs) remain lower than BEF 450. If infant vaccination is opted for, it would be appropriate to vaccinate 12-year-olds during the first eleven years as well, because the analysis shows that vaccination against hepatitis B is more favourable than doing nothing for both age categories. Results were sensitive to the discount rate, vaccine price, and assumptions on indirect cost. The positive results of this study were influenced by the relatively high sero-prevalence (7,6 %) that was used to calculate the annual attack rate.

TI: An economic evaluation of universal vaccination against hepatitis B virus.
AU: **Fenn-P; Gray-A; McGuire-A**
SO: J-Infect. **1996** May; 32(3): 197-204
AB: This report presents the results of an economic evaluation into a vaccination programme against Hepatitis B, utilising U.K. data. The study was performed from a societal

perspective. Cost-effectiveness ratios were calculated for four different programmes: an infant vaccination programme; a child vaccination programme (6-year olds); an adolescent vaccination programme (11-year olds); and a combined child and adolescent programme. For each programme, the number of annual cohorts vaccinated was varied from 1 to 25. The outcome was defined as incremental life years gained, and the results are reported as costs per incremental life-year gained. A Markov-cycle approach was used, with different transition probabilities for consecutive cohorts. This was done to accommodate the simulation of a herd immunity effect. Benefits were calculated in both undiscounted and discounted forms. All costs were discounted at 6 % discount rate. Baseline results with benefits discounted range from £ 227130 to £ 301365 per life year gained for a 25-year vaccination programme, depending on the vaccination strategy. With benefits undiscounted, the comparable range is from £ 5234 to £ 9646. For a 25-year vaccination campaign, the infant strategy was the most efficient strategy. All major epidemiological and cost assumptions were subjected to a sensitivity analysis. Results were sensitive to assumptions on incidence of HBV infection, the degree of underreporting, the risk to develop cirrhosis, and apparently, the discount rate. A major advantage of this study is that it was tried to accommodate for the herd immunity effect, making the results more realistic than in more static economic evaluations. However, the cost estimates were only based on length of stay in hospital, and therefore underestimates of real costs of HBV consequences. The study results leans heavily on the assumption that only 8.7 % of acute cases of HBV is being reported. A simple model for progression of disease after acute infection was used, in which infected persons are allowed to progress immediately to cirrhosis and liver cancer. This may also result in an overestimation of the benefits of vaccination.

TI: Vaccination against hepatitis B virus in Spain: a cost-effectiveness analysis
AU: **Garuz-R; Torrea-JL; Arnal-JM; Forcen-T; Trinxet-C; Anton-F; Antonanzas-F**
SO: Vaccine **1997**; 15 (15) : 1652-1660
AB: A cost-effectiveness analysis with a societal perspective was done to determine the outcomes of the following strategies of mass immunisation against hepatitis B in Spain, a country of intermediate endemicity: vaccination of adolescents, new-borns, both populations, and vaccination plus passive immunisation of new-borns of HBsAg positive mothers. Decision trees supported on Markov models with Monte Carlo simulation have been used for the calculation of costs of the disease and a mathematical model of differential equations was used for the simulation of the potential effectiveness of vaccination. Calculations were made for the census target population of 1993. Effects were simulated for periods of 10, 20 and 30 years. The costs considered were those associated with the vaccination and travel of subjects, diagnosis, and treatment of the disease. It was assumed that booster vaccinations were given after a period of 10 years. No indirect or intangible costs were incorporated in the study. Costs were discounted with a 5 % discount rate. Effects were discounted at 0, 5 and 10 percent. The results are presented as additional cost or saving per case of infection prevented. In all assumptions, results showed that the most effective strategy for mass vaccination was the

vaccination of adolescents. The combination of vaccinating all adolescents together with active and passive immunisation of children born to HBsAg positive mothers was even more cost-effective. Sensitivity analysis showed that results were most sensitive to vaccine price and less sensitive to disease costs, epidemiological assumptions and discount rate used.

TI: Hepatitis B immunization in a low-incidence province of Canada: comparing alternative strategies.
AU: **Wiebe-T; Fergusson-P; Horne-D; Shanahan-M; Macdonald-A; Heise-L; Roos-LL**
SO: Med-Decis-Making. **1997** Oct-Dec; 17(4): 472-82
AB: This study provides a comparative cost-effectiveness analysis of three universal immunisation programs for hepatitis B virus (HBV). The setting of the study is a low-incidence province of Canada, Manitoba. Using three theoretical cohorts of infants, 10-year-olds, and 12-year-olds, a universal immunisation program was compared with a prenatal screening/new-born immunisation program involving testing of pre-partum women and immunisation of new-borns of HBsAg-positive mothers. This screening program was maintained in all 3 universal vaccination scenarios. A Markov long-term outcome model used Manitoba data to estimate costs and health outcomes across the life-span. The model was based on an HBV incidence rate of 19/100,000 and incorporated the most recent treatment advances (interferon therapy). A discount rate of 5% was used for costs and effects. Cost-effectiveness is expressed in terms of cost per life year gained. The perspective of the study is that of a third-party payer. The universal infant-immunisation program was associated with a cost-effectiveness ratio of $15,900 (Canadian) per year of life saved. These figures were $97,600 and $184,800 (Canadian) for the universal programs for 10- and 12-year-olds, respectively. Cost-effectiveness ratios were found to be sensitive to changes in immunisation (vaccination) costs, HBV incidence rates, and the rate at which protective antibody levels are lost over time. This study leans heavily on the data provided by Krahn and Detsky (Med Decis Making 1993), and must be regarded an update (with more recent insights into the disease and its treatment incorporated) of the latter study.

TI: Costs and cost-effectiveness of a universal, school-based hepatitis B vaccination program
AU: **Krahn-M; Guasparini-R; Sherman-M; Detsky-AS**
SO: Am J Public Health **1998**; 88 (11) : 1638-1644
AB: This study evaluated the costs and cost-effectiveness of a school-based universal vaccination program against hepatitis B in which 12 year old adolescents are vaccinated. This program is effective as off 1994 in the Canadian province of British Columbia, which has a high incidence rate of 30 reported cases/100.000. This program is compared with the prior strategy of maternal screening and vaccination of offspring born to carrier mothers, in addition to vaccination of high-risk individuals. The study comprises both a descriptive cost study and a cost-effectiveness analysis of British Columbia’s vaccination program for 1994. Public

health nurses administer hepatitis B vaccine to grade 6 students in schools. Costs of vaccine, vaccine administration and net program costs were measured. A Markov model was used to calculate the cost-effectiveness of the program. A life-long time perspective was used both for costs and effects. The study reported both a societal and a third-party payer perspective. Vaccinating each student cost US$ 44, US$ 24 of which was the cost of vaccine administration. The net cost was $9 per person; considering productivity costs, net savings were US$ 75 per person. Marginal cost per life year gained of the adolescent strategy compared to the maternal screening + high risk strategy was US$ 2100. Future costs and life years were discounted at 3 %. Results were sensitive to total delivery costs of the vaccination strategy and very sensitive to incidence rates. This study is different from other studies because an annual rate of loss of vaccine immunity was modelled. Furthermore, costs of vaccination are studied in more detail as usually. The positive cost-effectiveness ratio of adolescent immunisation is heavily dependent on the high incidence rate in the province under study.

Appendix 6 Excluded Studies (in alphabetical order)

The following studies were excluded from the review as they did not meet the inclusion criteria:

1) Adler MW, Belsey EM, McCutchan JA, Mindel A. Should homosexuals be vaccinated against hepatitis B virus? Cost and benefit assessment. *Brit Med J* 1983; 286: 1621-1624
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4) Audet AM, Delage G, Remis RS. Screening for HBsAg in pregnant women: a cost analysis of the universal screening policy in the province of Quebec. *Can J Public Health* 1991; 82: 191-195
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6) Badia X, Nocea G, Rovira J. Differences in the methodology and data of economic evaluations of a health programme. The case of Hepatitis B vaccination programmes in Spain. *PharmacoEcon* 1997; 11: 175-183
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8) Bos CA. Hypothetical vaccination of the Dutch population with a herpes simplex virus vaccine: estimation of the profitability using a demographic projection model. *Vaccine* 1998; 6: 309-314
9) Botman MJ, Botterhuis JAM, De Krieger RA. Immunisatie tegen hepatitis B; kosten en baten in een Nederlands ziekenhuis. *Ned Tijdschr Geneeskd* 1984; 128: 1748-1752
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13) Dusheiko GM, Roberts JA. Treatment of chronic type B and C hepatitis with interferon alfa: an economic appraisal. *Hepatol* 1997; 22: 1863-1882
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16) Everett WD. Hepatitis B prevention strategies. A benefit-cost analysis of immune serum globulin, hepatitis B immune globulin, and hepatitis B vaccine in the military. *Am J Prev Med* 1986; 2: 359-366
17) Garcia de Ancos JL, Roberts JA, Dusheiko GM. An economic evaluation of the costs of α-interferon treatment of chronic active hepatitis due to hepatitis B or C virus. *J Hepatol* 1990; 11: S11-S18
18) Gesemann M, Gentner P, Scheiermann N. Hepatitis B vaccination of blood donors - a cost-benefit analysis. In: Sibrowski W, Stangel W, Wegener S (editors): Transfusionsmedizin 1994/94. Beitr Infusionsther Transfusionsmed. Basel: Karger 1994, Vol. 32: 110-112
19) Goldwater PN. History of hepatitis B vaccination in New Zealand: lessons for Australia? *Aust J Public Health* 1993; 17: 221-225
20) Hamilton JD. Hepatitis B virus vaccine. An analysis of its potential use in medical workers. *J Am Med Assoc* 1983; 250: 2145-2150
21) Hankins DG, Ebert KD, Siebold CM, Fuller TK, Frascone RJ, Campion BC. Hepatitis B vaccine and hepatitis B markers. Cost effectiveness of screening prehospital personnel. *Am J Emerg Med* 1987; 5: 205-206

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24) Holliday SM, Faulds D. Hepatitis B vaccine. A pharmacoeconomic evaluation of its use in the prevention of hepatitis B virus infection. *PharmacoEcons* 1994; 5: 141-171
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