General vaccination against hepatitis B revisited

Gezondheidsraad **President**
Health Council of the Netherlands

To the Minister of Health, Welfare and Sports

Subject : presentation of advisory report *General vaccination against hepatitis B revisited*
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Dear minister,

I hereby present you with the advisory report *General vaccination against hepatitis B rivisited*. The report was prepared by the National Immunisation Programme committee and was reviewed by the standing committees on Infection and Immunity, Medicine and Medical Ethics and Law.

The general advisory report of March 2007 entitled *The future of the national immunisation programme: towards a programme for all age groups (De toekomst van het Rijksvaccinatieprogramma: naar een programma voor alle leeftijden)* included a recommendation to assess, within the short term, the inclusion of a general vaccination against hepatitis B in the National Immunisation Programme. Earlier, in 1996 and 2001, Health Council reports had discussed the possibility of general vaccination against hepatitis B; however, general vaccination was not advised in 2001, because at the time the effectiveness of general vaccination could not be compared with the existing high-risk group based approach.

Besides the scientific aspects and uncertainties, there are considerations of a practical and moral nature. The committee therefore provides three vaccination scenarios, each associated with its own advantages, disadvantages and uncertainties. The committee favours the scenario in which general vaccination is provided to infant children in combination with a catch-up programme for 12-year-olds, as this combined programme offers the best health benefits. Vaccination amongst high-risk groups will have to continue for the time being, until these groups have been adequately protected by a general vaccination programme. I endorse the committee's analysis and conclusions.

Yours sincerely,
(signed)
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to:

the Minister of Health, Welfare and Sport

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The report in brief

Since 1989 the Netherlands has pursued a ‘high-risk group’ policy for vaccination against hepatitis B, because in comparison to other parts of the world the prevalence of hepatitis B is low in the Netherlands and incidence of the disease appears to be concentrated within these high-risk groups.

- Despite this intensive and focused policy, the incidence of the disease has not fallen a great deal.
- Moreover, no known risk factor is cited in a quarter of the reported cases of acute hepatitis B in the Netherlands.
- Certain high-risk groups are not being adequately reached, and the possibilities of increasing this reach are limited.
- A mathematical model has now been developed in which the effects of the present high-risk group policy can be compared with a general vaccination policy.
- The model estimates that, compared to the high-risk group policy, general vaccination could prevent more than twice as many hepatitis B virus infections and prevent a considerably greater number of mortalities.
- The vaccination of high-risk groups and general vaccination are both cost-effective approaches with respect to the usual standards.
- General vaccination could be delivered to infant or to prepubertal children. General vaccination for infants would probably deliver the greater health benefit, and it would also be easier to incorporate into the existing National Immunisation Programme. No additional injections are involved.
- Some uncertainty remains about the duration of protection after vaccination. This is important, because – especially after infant vaccination – protection is needed for decades.
- Both general vaccination scenarios meet the vaccination evaluation criteria of the National Immunisation Programme. However, the committee favours general vaccination for infant children in combination with an eleven-year catch-up vaccination programme for 12-year-olds.
- In the event that general vaccination for infant children is introduced, the duration of the protection conferred to these children should be monitored. In time, catch-up vaccination at 12 years of age can be replaced, if necessary, by a single booster injection.

Contents

Summary, conclusions and recommendations

The question is: should we retain the existing vaccination of high-risk groups, or implement supplementary general vaccination against hepatitis B?

In its 2007 report *The future of the National Immunisation Programme: towards a programme for all age groups* the Dutch Health Council carried out a preliminary selection from a large number of candidate vaccines. Further analysis was recommended for a limited number of vaccines, and for vaccination against hepatitis B the Council recommended that the effectiveness and appropriateness of directed hepatitis B vaccination programmes be evaluated and compared with a general vaccination programme. The present advisory report is the result of this evaluation and comparison.

Between 1983 and 2003 the Health Council advised on several occasions on vaccination against hepatitis B within the framework of public health programmes. As a result of its advisory reports, vaccination programmes have been set up to protect social groups having a raised risk of contracting hepatitis B: the children of mothers carrying the hepatitis B virus (HBV), certain patient groups, behavioural risk groups, medical and paramedical staff, and others running the risk of infection as a result of their professional work. After it had become clear during the 1990s that these various directed programmes did not have the reach that had been hoped for, implementation of the programme was intensified in a number of phases. In 2003 the package was extended to include the vaccination

of infants whose parents came from countries having intermediate or high levels of endemic disease.

The main reason that the Netherlands has opted for this ‘risk group’-oriented approach is the relatively low incidence of hepatitis B compared with other parts of the world, and the fact that hepatitis B occurs with greatest frequency within specific social groups which – up to a point – can be targeted. Other countries in North-Western Europe (the United Kingdom, the Scandinavian countries and Finland) operate similar policies; in this they depart from the advice given by the World Health Organization (WHO), which has recommended general vaccination.

Directed vaccination programmes have an expanded, but still inadequate range

In recent years the range of these directed programmes was expanded, particularly in order to include people in behaviour-linked risk groups: homosexual men, injecting drug users, heterosexual prostitutes and their clients and, until recently, heterosexuals undergoing sexually transmitted disease (STD) diagnosis and treatment. In Amsterdam the intensification of the direct approach method towards people in these risk groups led to a clear drop in the number of new and acute cases of hepatitis B. At the same time, it became clear that the reach of that programme as well was still limited with respect to the total numbers of people in these behavioural risk groups: in fact more than half of them turned out not to have been vaccinated.

The number of new infections and mortalities is not falling

In the Netherlands the number of reported cases of acute hepatitis B is at least three times as high amongst men as it is amongst women. In both groups the early 1980s saw a decline in incidence levels, with numbers stabilising over the following years. In the early 2000s there was a limited rise in incidence in men, and in recent years this has once again been followed by a decline to previous levels.

At national level, the intensification of this direct approach to people in high-risk groups has resulted in a slight fall in the number of new, acute cases of hepatitis B. At the moment the Netherlands deals with 200 to 300 reported cases of acute hepatitis B per year; and every year there are a few deaths from acute hepatitis B, and an average of 23 deaths as a result of chronic hepatitis B reported. However, these reported numbers are subject to underreporting. Most cases of

chronic hepatitis B concern infections which were contracted abroad and which would not have been prevented by a Dutch national vaccination programme; those carrying the disease are nonetheless contagious to others.

Vaccination against hepatitis B is effective, safe, and provides long-term protection

In 2006 the general vaccination of children against hepatitis B was carried out worldwide in most WHO member states. This means that there is extensive experience with the use of these vaccines. Large-scale research studies have shown that vaccination against hepatitis B is both effective and safe.

If protection during puberty is seen to be important for a section of the population, then we have to be reasonably certain that vaccination in infancy provides long-term protection. The general vaccination of prepubertal children instead of infants is another option, but this means setting up new contact moments for vaccination at an age for which the National Immunisation Programme (NIP) has, as yet, not been active. For girls, these contact moments could be combined with contact moments for vaccination against cervical cancer, but it is uncertain whether this approach would provide an adequate reach.

Although an increasing amount of data is becoming available on the long-term protection conferred by vaccination, this data does not yet yield absolute certainty. Functional immunity appears to be in place more than fifteen years after vaccination. Moreover, about 26 years after the first use of plasma vaccines and 20 years after the first use of recombinant vaccines, extremely few breakthrough infections have occurred. However, it has been reported that in the long term some individuals, especially if a low vaccine dose was employed, appear to lose immunological memory (as evidenced by the absence of rapid antibody formation after a booster injection). There have been only sporadic breakthrough infections amongst such people, and none has become chronically infected.

New model-based calculations: favourable cost-benefit ratio

In support of the advisory process, staff members of the National Institute for Public Health and the Environment (Rijksinstituut voor Volkgezondheid en Milieu or RIVM) have performed new model-based calculations in which the targeted vaccination programmes and general vaccination of infants or pre-teens are compared to each other. Estimates of the potential health gains show that the incidence of new hepatitis B infections may decrease by 44 percent in 50 year's time if the high-risk group policy is followed. A general vaccination strategy

would reduce the incidence over the same period of time by 90 percent. This would prevent an estimated 1,500 deaths in that time frame.

The cost-effectiveness ratio of such a general vaccination when added to the current approach to risk would be about 3,000 euros per Quality Adjusted Life Year (QALY) gained. The cost-effectiveness ratio is hardly dependent on the vaccine being given to infants or pre-teens. The cost-effectiveness ratio of general vaccination of pre-teens *is* dependent on the cost of introducing the necessary new contact moments for vaccination at this age.

RIVM also studied the cost-effectiveness of an eleven-year-long catch-up campaign among twelve year olds in addition to general vaccination of infants. Such a catch-up campaign should be capable of bringing the health benefits forward by more than ten years compared to the situation without a catch-up campaign. In addition, an estimated 500 deaths can be avoided over a period of 50 years. The cost-effectiveness ratio of such a catch-up campaign, if not combined with vaccination against cervical cancer for girls, would be about 8,300 euros per QALY gained. If combined with a vaccination against cervical cancer, the ratio would be approximately 6,875 euros per QALY gained.

Strategy considerations

The decision on which strategy to follow proves to be complex and difficult to make. In addition to scientific aspects, there are also considerations of a practical and moral nature. This is why the committee presents the various options and indicates its preferences, but makes no conclusive recommendations.

Continuation of the current risk policy exclusively

The current high-risk group approach has produced a number of important successes. The corpus of vaccination programmes targeted at specific high risk groups has a long history in the Netherlands, and a considerable reach in comparison with many other countries. Several of these programmes have been intensified to no small degree, especially in recent years. This has helped produce significant health gains through the years. Continuation of only the high-risk group approach would be preferable if it could be established that this approach is sufficiently effective. Despite great efforts, the current approach is still not adequate: there is limited evidence that intensification of vaccination programmes results in a reduction of the disease burden, and the effective range among the high-risk groups is limited, even with an intensive approach. It is uncertain if further intensification will be possible.

Expansion to general vaccination of infants

Far greater health benefits can be achieved through a programme that includes general vaccination of infants than by continuing with the current high-risk group approach only. High-risk individuals are then more likely to be vaccinated, and protection would extend beyond them as well. The hepatitis B vaccine is safe and effective. Expanding the vaccination programme along these lines is also cost effective.

In a practical sense, general vaccination can be easily introduced by replacing the current DPT-polio-Hib vaccine (against diphtheria, pertussis, tetanus, polio and *Haemophilus influenza* type b) by a combination vaccine including a hepatitis B component. The number of inoculations (two per contact moment) would remain the same. In the short term, the current hepatitis B vaccination could be discontinued for children with one or both parents from medium or high-endemic countries. In the long term, vaccination programmes targeted to people in behavioural risk groups could be discontinued as well. The actual risk reduction, however, will only be truly significant once the vaccinated children grow past the age at which these risks predominantly occur, in other words about twenty to thirty years from now.

Also in the future people will demand individual protection against occupational risks and will want to continue vaccinating those concerned, regardless of their age, if they are not protected by prior inoculation.

Expansion to general vaccination of prepubertals

Expanding current policy to include general vaccination of prepubertals can also produce significant health gains. This strategy is also better suited to reach high-risk individuals and others compared to the current high-risk group approach. Vaccinating people as close as possible to the age at which they become sexually active offers the relevant protection at the most propitious moment, mitigating the concerns about the duration of effective protection that arise where infant vaccination is concerned.

Another advantage of this programme is that vaccination of adults from high-risk groups can ultimately be discontinued. However, vaccination of children with at least one parent from a medium or high-endemic country must be continued if general vaccination of pre-teens is opted. If general vaccination of pre-teens is the option of choice, then the committee recommends a simultaneous vaccination for girls against hepatitis B and cervical cancer.

One problem of the pre-teen approach is that infections that occur between zero and twelve years cannot be prevented. These infections are often asymptomatic. They are therefore not reported and especially young children have a high potential of becoming carrier. The programme also requires establishing new contact moments, and there is some uncertainty about the associated costs. These costs have a significant impact on the overall cost-effectiveness of the programme. Finally, the uptake of vaccination is less certain than in the case of vaccination of infants.

The committee's preference

Both general vaccination scenarios meet the assessment criteria for the National Vaccination Programme. However, the committee would prefer a programme that includes general vaccination of infants. The committee recommends that an eleven-year catch-up campaign be organised for twelve-year-olds, when general vaccination of infants is being implemented. This ensures that, every year, a cohort of twelve-year-olds receives protection against hepatitis B and substantial beneficial effects of vaccination will be obtained earlier.

The current risk policy must be continued

The committee wishes to stress that, when general vaccination is introduced, pregnant women should continue to be screened for carriership of the hepatitis B virus (HBsAg-positive) and the newborn babies of HBsAg-positive mothers should continue to be vaccinated. This protocol is intended for people who have already contracted the virus and who are at serious risk of chronic infection and carriership. It consists of an initial vaccination directly after the birth and the administration – also as soon as possible after the birth – of directly protective antibodies, otherwise known as passive immunisation. It is imperative to vaccinate the children of carrier mothers. The vaccination of adults in behavioural risk groups will also have to be continued for many years after the introduction of the general vaccination until people in these risk groups are protected by the general programme.

A catch-up campaign is relevant

If general vaccination is introduced for infants, the committee recommends that an eleven-year catch-up campaign be organised among twelve-year-olds to raise immunity in the population to a relatively high level. This will also help to rea-

lise the anticipated health benefits more than ten years ahead of time and further increase the benefits at relatively minor extra expense. A catch-up campaign would also respond to the crucial need for protection at as young an age as possible; it reduces the chance of carrier ship and chronic infection later in life. Given that the virus in the general population is transmitted mainly through sexual contact, a catch-up campaign would ensure protection relatively quickly in the age groups where sexual transmission is most likely to occur.

The committee recommends that, for girls, the catch-up campaign be carried out at the same time as the vaccination programme against cervical cancer.

Monitoring effectiveness, safety and the immunological memory

As in all public vaccination programmes, it is essential to monitor effectiveness. A monitor should be set up to ascertain the incidence of breakthrough infections among vaccinated children. Besides the usual passive registration of side-effects, the committee advises setting up a link between vaccination registers and disease registers so that any infrequent side-effects can be tracked.

Once the first group of vaccinated infants reaches the age of twelve and their immunological memory clearly points to long-term protection, the catch-up campaign can be terminated. If functional immunity leaves much to be desired eleven years after infant vaccination, the catch-up campaign can be converted into a booster injection for twelve-year-olds. To determine whether vaccination at the age of twelve can be discontinued, in-depth immunological research will have to be performed on some of the twelve-year-olds who were vaccinated as babies. This research will have to look not only at the antibody titres but also at functional immunity – in the form of, for example, the capacity to elicit a fast immune response with a booster injection of the hepatitis B vaccine – in order to demonstrate immunological memory.

Information

The committee advises that an information campaign be set up to communicate the importance of the vaccination. The committee has identified several target groups that require a special approach: parents of newborns, parents of pre-teens, and pre-teens themselves.

It is important for youth healthcare workers to supply parents with proper and adequate information. In order to do so, they need knowledge of hepatitis B and good communicative skills to parents and their children. Training courses and refresher courses should take this into account.

In the Netherlands HBV is often transmitted by sexual contact. Special information kits should therefore be compiled for parents and twelve-year-olds from groups with different cultural, ethnic and religious backgrounds

Chapter 1

Introduction

1.1 Background to this advisory report

Vaccination against hepatitis B: a high-risk group approach or general vaccination?

Vaccines against hepatitis B became available, at first on only a limited scale, in the early 1980s. In the years that followed, the Health Council published a number of advisory reports on their inclusion into public vaccination programmes.[1-3] Up to now it has always advised a high-risk group based approach, in which only those people were vaccinated who ran a relatively higher risk of contracting hepatitis B. In 1992 the World Health Organisation (WHO) advised that general vaccination include a hepatitis B vaccine, even in countries in which the disease had a low prevalence. However, the Netherlands continued to adhere to its high-risk group based approach.

The most important reason for maintaining a high-risk group based approach was the relatively low prevalence of the disease in the Netherlands, which meant that vaccination was considered irrelevant for the great majority of the population. Because high-risk groups could be reached relatively easily in the Netherlands, it was held that general vaccination to protect the population as a whole, including high-risk groups, was unnecessary. The same approach was adopted in several other countries having a low prevalence of hepatitis B, such as the United Kingdom (UK), the Scandinavian countries and Finland.

However, in 2007 the Health Council recommended the re-evaluation of general vaccination against hepatitis B. The costs and effects of the existing high-risk group based approach would have to be compared with those of general vaccination. In the present report, the Council carries out this analysis. The various approaches are reviewed with respect to the assessment framework and seven criteria for the inclusion of vaccinations in public programmes which the Council drew up in 2007 and which have been adopted by the Minister of Health, Welfare and Sport (VWS).[4]

New calculation models enable comparison

In its 2007 report *The future of the National Immunisation Programme: towards a programme for all age groups* (*De toekomst van het Rijksvaccinatieprogramma: naar een programma voor alle leeftijden*) the Health Council provided an evaluation of the current high-risk group based approach towards vaccination against hepatitis B. At the end of 2007 the first calculations carried out by the National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu or RIVM) were published; these modelled a number of different approaches and compared the resulting effects and costs. In the course of 2008 the RIVM performed additional calculations at the committee's request. Partly on the basis of the resulting reports, the Health Council is now in a position to answer the question of whether the existing risk-based approach is adequate to the task of tackling hepatitis B in the Netherlands, or whether a programme is needed which includes general vaccination.

General vaccination against hepatitis B: for infant or prepubertal children?

Besides the question of whether to vaccinate only high-risk groups or the population as a whole, there is the issue of whether general vaccination can be given best to infant children or to prepubertal children. The WHO recommends the vaccination of infants in all countries. In 2006, the general vaccination of children against hepatitis B was carried out in 164 of the (then) 192 WHO member states. This has yielded extensive experience with the use of the vaccines. The inhabitants of countries with a low prevalence of hepatitis B run little risk of contracting the disease before puberty; in these countries, including the Netherlands, the virus is generally spread through sexual contact. This was the reason the Council recommended in 2001 that the vaccination of infants should not be general, but only for children with one or both parents from a country having intermediate or high endemic, as children with parents from these countries have a

higher risk of encountering virus carriers and becoming chronically infected in turn. These children have a direct interest in vaccination against hepatitis B as infants. In the Netherlands, since 2003 infant children with one or both parents from high-risk countries have been vaccinated against hepatitis B following a four-stage protocol: at the age of two, three, four and eleven months.

The costs of general infant vaccination did not constitute a reason for the Council to advise against its implementation: according to the Council's analysis, the cost-effectiveness of such a programme lay within the conventional limits of acceptability.[1]

For the great majority of the population of the Netherlands, vaccination is only relevant from the age of puberty onwards. The best way to confer protection against hepatitis B would be to vaccinate shortly before then, for example at the age of eleven or twelve. For this reason, some countries have introduced the general vaccination of schoolchildren against hepatitis B. Switzerland vaccinates children aged between 11 and 15, Hungary vaccinates 14-year-olds, and Slovenia vaccinates children between the ages of 5 and 6. In the Netherlands, the Health Council judged in 2001 that the interests of general vaccination against hepatitis B for all prepubertal children could not be justified on the basis of the health data then available.

The duration of protection

Besides the above-mentioned reasons for not implementing a general vaccination programme, another consideration was the uncertainty of the duration of the protection conferred by vaccination. Experience with hepatitis B vaccination was then less extensive than it is now, and it was not clear whether vaccination continued to confer adequate protection more than 15 years after it was given – at exactly the time that this protection would become most relevant.

In the meantime we can draw on a much longer period of practical experience with both single and combined vaccines against hepatitis B. There are no clear indications that the protection they confer diminishes over time.

Would general vaccination make a catch-up vaccination programme desirable?

In the present report the Health Council once again assesses the desirability of general vaccination against hepatitis B in comparison with the existing high-risk group based approach. If this analysis were to favour general vaccination, then it would become a relevant question to what extent its effects should be increased

and expedited by carrying out a ‘catch-up’ vaccination campaign amongst those who fall outside the primary target age groups.

A catch-up vaccination campaign can increase the effectiveness of a general vaccination programme if it means that the age group facing the greatest risks of contracting hepatitis B are thereby given vaccine protection more quickly. This is particularly true of a general infant vaccination programme.

If the decision were to be taken to adopt a general infant vaccination programme, then a suitable moment to direct a possible catch-up vaccination campaign would be early puberty.

Could parts of the existing vaccination programme be halted?

If the decision were taken to introduce general vaccination against hepatitis B, could all existing, directed vaccination programmes then be stopped?

The answer to this is no. Certain programmes could become redundant in the long term, but others will have to be continued for the time being. The risk of contracting hepatitis B is distributed across different age moments, and it will be a while before a general vaccination programme can be said to protect against all these risks.

A general hepatitis B vaccination programme has, as has been described, two options: to vaccinate infant or prepubertal children. Each choice has its own consequences: for instance, the current vaccination of infant children with at least one parent from an intermediate or high-endemic country could be dropped if a general infant vaccination programme took its place, but it would have to be continued if the general programme were to target prepubertal children.

The vaccination of the children of hepatitis B virus carriers is a question not of primary prevention but of treatment (secondary prevention). This vaccination has been included in the National Immunisation Programme (NIP) for pragmatic reasons, but it is of considerable importance, and the question of whether it can be responsibly subsumed into a general programme in this way deserves special attention.

1.2 The request for advice

Taken overall, the present advisory report addresses the following questions:

1 What would be the best approach to tackling hepatitis B in the Netherlands: the existing vaccination of people in high-risk groups, or a programme which also includes general vaccination?

2 What are the latest insights into the duration of protection after vaccination against hepatitis B? Under which conditions are booster vaccinations deemed to be necessary?
3 If general vaccination is considered advisable, is it best to vaccinate infant children or prepubertal children?
4 Would a catch-up vaccination campaign be advisable alongside a general vaccination programme? What scale of catch-up campaign would be advised?
5 If a programme were adopted which included general vaccination, which components of the existing high-risk group based programme could then become redundant? Which components would have to be retained for the time being even if general vaccination were introduced?

The background to this advisory report is given in Annex A.

1.3 Committee, working methods and task delineation

The task of answering these questions was assumed by the National Immunisation Programme committee (*commissie Rijksvaccinatieprogramma*), which was convened on 3 April 2007 by the chairman of the Health Council for a further five-year period. The membership of the committee is detailed in Annex B. The committee studied the scientific literature on hepatitis B and vaccination against hepatitis B in order to collect all relevant scientific knowledge on the subject. It also consulted experts both at home and abroad; an overview of these consultations is given in Annex B. In support of the committee's advice, the RIVM carried out a number of supplementary cost-effectiveness analyses in which the costs and effects of three different approaches to vaccination against hepatitis B were calculated. The three scenarios were:
1 the existing, high-risk group based approach;
2 the existing, high-risk group based approach supplemented by the general vaccination of infant children;
3 the existing, high-risk group based approach supplemented by the general vaccination of prepubertal children.

For the second scenario, a catch-up vaccination campaign for prepubertal children was included in the calculations.

Finally, the findings for the three scenarios were reviewed with respect to the seven criteria for the inclusion of a vaccination in a public programme.

1.4 Summary of chapter contents

Chapter 2 summarises the history of earlier advisory reports published by the Health Council on the prevention of hepatitis B. Chapter 3 gives a general description of hepatitis B, an overview of the available vaccines, and considers the international scientific literature on vaccination against hepatitis B. It also reviews the current status of general vaccination programmes in those Western European countries which currently employ a high-risk group based approach. In Chapter 4 the committee lays out the evaluation framework and clarifies the seven criteria used for vaccine inclusion in a national vaccination programme.

In the subsequent six chapters the committee reviews hepatitis B vaccination by reference to the three scenarios just described and the seven vaccination programme inclusion criteria: the seriousness and extent of the disease burden (Chapter 5), the effectiveness of the vaccination (Chapter 6), safety issues (Chapter 7), the acceptability of vaccination to the individual and to the NIP as a whole (Chapter 8), and the questions of efficiency (Chapter 9) and urgency (Chapter 10).

In Chapter 11 the committee reviews the advantages, disadvantages and uncertainties of each of the three scenarios and expresses its own preference. Finally, in Chapter 12 the committee discusses a number of aspects of general vaccination programme implementation. This includes which programme components of the existing high-risk group approach might become redundant if a general vaccination programme were to be adopted, and which programme components would have to be retained for the time being. Attention is also given to the requirements with which public information provision on vaccination against hepatitis B would have to comply, and to the question of monitoring effectiveness and safety.

Chapter 2

Vaccination programmes against hepatitis B in the Netherlands

In the Netherlands, vaccination against hepatitis B has been used in high-risk groups for many years, and these vaccination programmes are regularly updated. This chapter provides an overview of this situation.

2.1 Early stages: the vaccination of specific groups

When the first vaccine against hepatitis B became available in the early 1980s, this represented the first-ever opportunity to protect people against hepatitis B virus (HBV) infection and carrier status. Partly because the vaccine was at first available in only limited quantities, a high-risk group based approach was adopted. In 1983 the Health Council published an advisory report on the groups to be vaccinated; these groups are summarised in Table 1 below.[2]

Table 1 Target groups for vaccination against hepatitis B according to the Health Council report of 1983. (Source: Health Council, 1996.)

Patients:
• haemodialysis patients;
• haemophilia patients and other patients for whom it may be expected that they will receive blood or blood products regularly or in large quantities
• mentally handicapped persons residing in institutions
Healthy persons:
• the sexual partners of HBsAg-positive persons
• neonates of HBsAg-positive mothers

- those exposed to infection through wounds caused by objects contaminated with HBsAg-positive or HBsAg-suspect blood
- male homosexuals having a wide variety of sexual contacts
- prostitutes and their clients
- persons whose professional work brings them into long-term contact with primitive living conditions in areas having a high prevalence of hepatitis B
- intravenous drug users

Medical and paramedical staff:

- doctors, nurses and paramedics who come into frequent contact with blood
- pathological anatomists and their staff, working with non-fixed and potentially infected material
- the staff of haemodialysis departments directly involved in patient care or the handling of haemodialytic equipment, including technical maintenance staff
- the staff of diagnostic and research laboratories coming into regular contact with blood or blood products
- midwives and maternity nurses
- dentists, dental hygienists, dental assistants and those indirectly involved in dental patient care who run the risk of infection

2.2 The late 1980s: screening pregnant women for carrier status

The treatment of neonates of women who carry the virus is actually a post-exposure treatment, since the children born of carriers (HBsAg-positive persons) are already infected. In the absence of curative vaccination these children have a 15 to 90 percent chance of contracting hepatitis B, and in this group the disease follows an almost invariably chronic course. However, vaccination can prevent the disease and its sequelae in almost all cases.

However, the directed vaccination of specific groups only partly reaches pregnant women carrying HBV. For this reason, in the 1980s trials were carried out in which all pregnant women were screened for carrier status. This showed that an average of 0.7 percent of the pregnant women in the trial regions – Rotterdam, Utrecht, Twente and the Gelderse Achterhoek – were carriers. Carrier status appeared with greater frequency in urban areas than in rural ones, and was more likely in women who had been born outside the Netherlands than amongst the indigenous Dutch. If the woman was found to be a carrier, her newborn child was given protective antibodies and vaccine.[5]

Following these trials, in 1989 a national programme was set up which screened all pregnant women for hepatitis B virus carrier status during the twelfth week of pregnancy. If the mother was a carrier, her child was given both active and passive protection as soon as possible after birth by administering hepatitis B antibodies and vaccine. In the course of this national screening, 0.44 percent of the pregnant women turned out to be carriers.[6]

In order to achieve the greatest possible coverage, at that time a choice was made to have the active immunisation of carriers' children take place simultaneously with the basic vaccinations carried out within the NIP. These were originally given at 3, 4, 5 and 11 months; later this was brought forward to 2, 3, 4 and 11 months, in combination with a large dose of antibodies at birth. Between 2003 and 2006, a (non-scientifically determined) schedule was followed which gave antibodies as soon as possible after birth, followed by the administration of vaccine at 2, 4 and 11 months. From 2006, the midwife or gynaecologist supervising the birth has had to administer the child's first vaccine dose as soon as possible after birth, at the same moment that antibodies are given to confer immediate protection. In this way, vaccinations against hepatitis B in this group have since been given at 0, 2, 3, 4 and 11 months.

2.3 The 1990s: intensifying the high-risk group based approach

In 1996 the Health Council published a report which assessed the degree to which the recommendations that it had made in its 1983 report were being followed. The report made it clear that the 1983 recommendations had not being put into large-scale practice, for reasons which had to do with funding and ambiguity about the implementation.

The quality of implementation of the vaccination programmes directed towards the various target groups was evaluated and placed into one of three categories: good, moderate and inadequate. Only for a few target groups could it be said that the implementation had been good; the overall situation is summed up in Table 2 below.

Table 2 Evaluation of the implementation of vaccination programmes against hepatitis B in the Netherlands in 1996. (Source: Health Council, 1996.)

Good implementation:
• haemodialysis patients
• haemophilia patients
• medical and dentistry students
Moderate implementation:
• mentally handicapped persons residing in institutions
• neonates of HBsAg-positive mothers
• those exposed to infection through wounds caused by objects contaminated with HBsAg-positive or HBsAg-suspect blood
• persons whose professional work brings them into long-term contact with primitive living conditions in areas having a high prevalence of hepatitis B
• medical and paramedical staff, including medical analysts, nurses, maternity nurses, and those involved in dental patient care

Inadequate implementation:

- the sexual partners of HBsAg-positive persons
- male homosexuals having a wide variety of sexual contacts
- prostitutes
- intravenous drug users

The report defined new target groups for vaccination, such as persons with Down's Syndrome, the housemates and family members of virus carriers, children up to the age of seven (since extended to the age of 19) in centres for asylum-seekers, persons with a variety of sexual heterosexual contacts already being treated in clinics for sexually transmitted diseases (STDs), paramedical and perimedical staff and persons training for professions in the sector, inasmuch as their work brings them into contact with blood.[2]

The Health Council concluded that an intensification of the high-risk group approach was needed in order to achieve higher vaccination coverage levels and improved protection of the target groups. Its report also set out the conditions under which general vaccination against hepatitis B could be introduced. It would have to be incorporated into the NIP; an adequate dose of HBsAg would have to be given, if possible in a combined vaccine; and the costs of the vaccine would have to be acceptable.[2]

2.4 Around the year 2000: the discussion of general vaccination

By 1992 the WHO had called for the worldwide introduction of general vaccination against hepatitis B, including in countries with a low prevalence of the disease. The call led to wide debate, including in the Netherlands. The RIVM had calculated that the cost-effectiveness of such general vaccination was unfavourable in the Netherlands.[7] One important observation in this analysis was that the large majority of HBV carriers in the Netherlands had become infected abroad and had arrived in the country via immigration; general vaccination in the Netherlands would not prevent infection and carrier status in such cases. The carriers themselves, however, are contagious to others.

The Dutch House of Representatives was of the opinion that the Minister of VWS ought to carry out the WHO's recommendations. In 2000 the Minister therefore asked the Health Council to advise on the incorporation of general vaccination against hepatitis B into the NIP. The Minister also asked the Council to give due attention to any negative effects that general hepatitis B vaccination might have on participation rates in the NIP, and to examine the question whether

it was better, given the duration of protection conferred by the vaccine, to administer general vaccination to children in infancy or later in childhood.

In its report of March 2003 the Health Council concluded that it was important to distinguish between two subpopulations within the population of the Netherlands. Children with at least one parent from a country where hepatitis B is relatively prevalent (more than 2 percent having carrier status) have a greater likelihood of coming into contact with a carrier, whether this was within their family, their social environment in the Netherlands, or during visits to the country of origin of the parent(s). About 15 percent of all neonates in the Netherlands belong to this subpopulation. Because the chance of developing carrier status is much higher for an infected child than an infected adult, this has a disproportionate effect on the total numbers of carriers. The only way to mitigate this effect is to administer general vaccination during infancy, and the Council therefore recommended that this be introduced for this subpopulation.

In families in which neither parent comes from a country in which hepatitis B is relatively prevalent, children below the age of about 12 generally run a small risk of infection with the disease. General infant vaccination of this part of the population was therefore deemed unnecessary.[1]

Revised calculations by the RIVM confirmed the importance of vaccination during infancy for the subpopulation of children with a raised risk of infection, and the minister adopted the recommendation to introduce vaccination for the infant children of parents who came from countries with a relatively high prevalence of hepatitis B.

The council did not recommend general vaccination of all infants, because in families where the parents do not come from countries with a high prevalence of hepatitis B, children below the age of about 12 generally run a small risk of contracting the disease, and because it was technically possible, thanks to the Dutch Municipal Records (*Gemeentelijke Basisadministratie*) system, to vaccinate only those children whose parents came from countries with a relatively high prevalence of hepatitis B. The Council did advise that after three years it should be determined whether the vaccination coverage in the subpopulation concerned had been adequate. This evaluation has since been carried out by the RIVM (see Section 6.4).[8]

In the rest of the general population, viral infection occurs principally through sexual contact. Because of uncertainties about the duration of the protection conferred by vaccination, it was the Council's judgement that it would make more sense to vaccinate at some point between the ages of 9 and 12; however, at the time the report was published, in 2003, insufficient data was available to

judge infection risk and the effectiveness of vaccination. The Council therefore advised that the RIVM be commissioned to refine existing epidemiological models of HBV and the effects of its vaccination strategies, so that these models could be used to compare the effects of the general vaccination of 9 to 12-year-olds with existing high-risk group based vaccination programmes.

The RIVM was subsequently commissioned to do so, and the first report of its comparative modelling research was published in late 2007. After consideration of this report by the committee, during which there was some scientific discussion of the interpretation of the results, supplementary results were made available to the committee in 2008. These results are discussed in Chapter 9.

2.5 Programmes for behavioural high-risk groups

As part of the implementation of the 1996 recommendation to intensify the high-risk group based approach, in 2002 separate programmes were launched to target so-called 'behavioural' high-risk groups. By this was meant the group of healthy persons who run the risk of HBV infection as a result of their sexual behaviour or, amongst intravenous drug users, through the shared use of needles or injection materials.

On the basis of these programmes homosexual men, heterosexual men and women with a variety of sexual contacts, prostitutes, their clients, and intravenous drug users all qualified for free vaccination. A number of outreach programmes were set up on behalf of these groups; for instance, homosexual men were approached via places of entertainment and meeting spots, and heterosexuals via outpatients' clinics for STDs.

This vaccination policy was evaluated in early 2007 during an expert meeting held by the Dutch Municipal Health Services (Gemeente GezondheidsDienst Nederland or GGD) and the Centre for Infectious Disease Control (Centrum Infectieziektebestrijding or CIb). This evaluation resulted in the recommendation to halt the vaccination of heterosexuals with a variety of sexual contacts. This recommendation was based on molecular epidemiological research findings that in the Netherlands, heterosexual contacts were not responsible for an infection chain of any importance. This advice was adopted by the Ministry of VWS, and the vaccination of heterosexual men and women with a variety of sexual contacts was stopped on 1 November 2007.[9]

Chapter 3

Hepatitis B and vaccines: the scientific position

This chapter gives an overview of general scientific data on the disease of hepatitis B, its treatment, vaccines against the virus, and the efficacy and effectiveness of these vaccines. An important aspect of the vaccination discussion is the duration of the protection conferred by vaccination. Finally, a brief review is provided of the status of vaccination against hepatitis B in other Western European countries employing a high-risk group based policy.

3.1 The virus and infection

HBV belongs to the hepadnavirus family. It reproduces in the liver and can cause liver dysfunction. The virus is contagious and is transmitted principally through contact with infected blood or unsafe sexual contact. The virus can occur in high concentrations in blood and serum and in lower concentrations in sperm, vaginal secretions and saliva. It is also found in tear fluid, urine and mucus, but the significance of this is unclear. The most important primary infection routes are from mother to child shortly before, during or after birth (perinatal), sexual contact, blood-blood contact (percutaneous), and through intensive contact between carriers and young children (known as 'horizontal' transmission).[10,11]

The virus carries the surface antigen HbsAg on its outer surface, and the presence of this protein in the blood indicates active HBV infection. If HBsAg has been demonstrably present for over six months, this is said to constitute a chronic HBV infection. The absence of HBsAg and the presence of antibodies against

HBsAg (anti-HBs) indicate immunity. If antibodies for the core protein of HBV (anti-HBc) are also present, then this means the subject has recovered from an HBV infection. If only anti-HBs are present, this therefore probably represents an immunity conferred by vaccination.

3.2 Hepatitis B infection

By ‘acute hepatitis B’ is meant the clinical picture after recent infection with, or the reactivation of, the virus. Chronic HBV infection (whether symptomatic or asymptomatic) can arise if the immune system is unable to remove the virus. As has been mentioned, an HBV infection is said to be chronic if the infection has been present for longer than six months.

The likelihood that a recent infection develops into a chronic hepatitis B infection, or ‘carrier status’, depends strongly on the age of the infected person. The younger the age at infection, the greater the chance that this will develop into carrier status (see Table 3). This explains the great importance of providing protection to young children. The risks of infection are greatest of all for newborn babies; 90 percent of infected newborn babies go on to develop carrier status.

An infection which becomes chronic often produces no immediate complaints. Of infected children below the age of six, 5-15 percent show symptoms of the illness, compared with 33-50 percent amongst older children and adults.[12] However, carrier status can have serious long-term consequences, particularly liver cirrhosis and liver cancer.[11,13] Because carriers remain contagious they play a significant role in spreading the virus.

Table 3 Percentage likelihood of the development of carrier status after primary infection with the hepatitis B virus as a function of age at infection. (Source: Vaccines, 4th edition, 2004.)

Age (years)	Likelihood of carrier status after infection
0-1	+/- 90 percent
1-4	+/- 60-30 percent
5-10	+/- 30-20 percent
15	+/- 10 percent
20 and older	+/- 5 percent

3.2.1 Acute hepatitis B

The clinical symptoms of acute hepatitis B strongly resemble those of other forms of viral hepatitis, and laboratory analysis is required to establish the particular variety of hepatitis concerned.

If symptoms appear, then this is generally after an incubation period of between six weeks and six months: malaise, lack of appetite, nausea, vomiting, fever, jaundice, muscle pain and fatigue are typical. The clinical symptoms of acute hepatitis B generally disappear within one to three months.

5 to 10 percent of patients also display symptoms similar to serum disease, characterised by joint pain or inflammation and skin rashes (including blisters). Other symptoms of acute hepatitis B can include infections of the intermediate and larger arteries (polyarteritis nodosa), kidney problems following damage to the capillary glomeruli in the kidneys (glomerulonephritis), the Gianotti-Crosti syndrome (a transient, benign rash on the arms, buttocks, legs and face) and aplastic anaemia, but these are rare.

Acute liver failure, also known as fulminant hepatitis, occurs in about 0.5 to 1 percent of infected adults and extremely rarely in infected infants and children. The mortality percentage of this serious disorder is high, between 60 and 70 percent, unless a liver transplant can be carried out and / or antiviral treatment administered.[1,11,14,15]

3.2.2 *Chronic hepatitis B*

Whether or not chronic infection with the hepatitis B virus displays clinical symptoms depends on the phase of the infection. Chronic infection can present in one of four phases:

1 In the *immune tolerant phase* there is a great deal of virus present in the blood (high HBV-DNA levels), and the hepatitis e-antigen (HBeAg), which indicates viral replication, is positive. However, there are no indications of liver infection: levels of serum alanine aminotransferase (ALAT), which indicates liver damage, are not raised. This phase generally lasts from 10 to 30 years.
2 The *immune active phase* also shows active viral replication (HBeAg positive, high HBV-DNA levels), but now there is also active infection of the liver, expressed in a raised ALAT level.
3 Transition to the *inactive phase* is characterised by a fall in the amount of virus (HBV-DNA) in the blood and by the formation of antibodies against the HBe-antigen (anti-HBe). This phase is therefore characterised by low HBV-DNA concentrations, a negative HBeAg and a normalised ALAT. Although viral replication continues, this is strongly suppressed by the host's immune system.

4 In some patients, a reactivated level of infection-related activity indicates a return to high virus concentrations in the blood. These patients develop an active HBeAg-negative chronic hepatitis called the *reactivation phase*.

Complaints include fatigue, reduced appetite, nausea, joint pain, stomach pain and jaundice.[12]

Chronically infected people run a serious risk of dying of HBV-related disorders. The WHO has estimated this risk as being between 15 and 25 percent worldwide.[13]

In 2006 it was estimated that hepatitis B was one of the most frequent underlying causes of cirrhosis (30 percent) and of liver cancer (53 percent) worldwide.[16] Every year, an average of 6 percent of chronically HBV-infected patients in the Netherlands develop cirrhosis. There is a close correlation between cirrhosis and hepatocellular carcinoma (HCC), and the presence of cirrhosis predisposes for the development of HCC. The great majority (80-90 percent) of HCC patients has an underlying cirrhosis.[11,17,18] Carriers of the hepatitis B virus must in principle always be regarded as contagious to others; however, the degree of this contagiousness varies strongly, depending on the phase in which the patient is found. The phases in which the viraemia is high and HBeAg is present are characterised by a higher risk of contagion.[19,20]

Liver cirrhosis is characterised by the death of liver cells and the formation of fibrous scar tissue. Cirrhosis leads to the gradual degradation of liver function, and eventually to liver failure. Early liver cancer has no typical symptoms. In more advanced stages symptoms include fatigue, nausea, reduced appetite, weight loss, liver enlargement and a swollen stomach, pain in the upper abdomen, and jaundice.[21]

3.3 The treatment of acute and chronic hepatitis B

Although important progress has recently been made, the treatment of hepatitis B remains comparatively problematic. There are no drugs with which to treat acute hepatitis B; its treatment is symptomatic. Researchers have, however, reported that the treatment of serious acute or fulminant hepatitis B with antiviral drugs offers a better chance of recovery.[15,22]

The progress which has been made chiefly concerns the treatment of chronic hepatitis B. Antiviral drugs have become available which impede viral replication, thereby mitigating liver damage. These drugs include PolyEthyleneGlycol

(PEG)-interferon and nucleotide and nucleoside analogues. Treatment with PEG-interferon results in HBeAg reduction in about 35 percent of cases; this reduction is permanent in 80-86 percent of HBeAg-positive patients. A complete cure (HBsAg absence) occurs relatively infrequently; 3-7 percent of those treated become HBsAg-negative.[18,23-25]

Interferon treatment has frequent (more than 30 percent of treatments) adverse side effects, including flu-like symptoms, fatigue and insomnia. Between 1-30 percent of those treated suffer from reduced appetite, loss of taste function, hair loss, concentration disturbances, emotional instability, depression, the induction of auto-immune illnesses and a low blood cell count (cytopenia). Sporadic adverse side effects (less than 1 percent of treatments) include nerve damage (polyneuropathy), paranoia or suicidal tendencies, retinal damage (retinopathy), hearing disturbances, epilepsy, loss of libido, and cardiotoxicity.[18]

Nucleoside and nucleotide analogues are employed when there is little likelihood of successful treatment with interferon, for instance if the patient cannot tolerate interferon or if a year-long interferon treatment has had no effect.[24] However, these drugs often have to be taken for the rest of the patient's life; virus replication resumes as soon as the medication is interrupted. Treatment with analogues can lead to drug resistance, characterised by virological breakthrough and raised ALAT levels which also indicate liver damage.[26]

There are a number of methods to determine whether a treatment regime is having an effect, including the normalisation of liver functions, the termination of active virus replication, and the clinical disappearance of HBsAg. Liver cirrhosis, however, once started, can only be treated symptomatically. To prevent, as far as possible, any further damage to the liver, the patient must be persuaded to stop drinking alcohol, to follow a diet, to submit to further treatment for hepatitis B using interferon or nucleoside and / or nucleotide analogues, and to undergo treatment for any other symptoms of cirrhosis.

Several methods are available in the treatment of liver cancer. The choice depends on the stage of the disease and on the age and general condition of the patient. In the first instance there is the option of removing part of the liver including the tumour. In some cases, however, a liver transplant will be needed. If the tumour cannot be surgically removed, chemotherapy or embolisation (the blocking of blood vessels to the tumour, leading to its oxygen and nutrition starvation) are other options.

3.4 Global illness and mortality following HBV infection

In 2004 the WHO estimated that the number of people with a present or past HBV infection was two billion – one-third of the entire global population. About 360 million people are chronically infected and run a raised risk of liver cirrhosis and liver cancer, disorders which are jointly responsible for 500,000 to 700,000 mortalities per year.

With regard to the prevalence of chronic hepatitis B, the world can be divided into three parts: areas with a high prevalence (more than 8 percent), areas with an intermediate prevalence (between 2 and 8 percent) and areas with a low prevalence (less than 2 percent).

High-prevalence areas include Africa, South-east and East Asia (except Japan and India), most of the countries of the Middle East, the Pacific, areas within the Amazon basin, and parts of the Caribbean.

Areas with intermediate prevalence cover most of the world: Central and South-west Asia, Eastern and Southern Europe, the Russian Federation, and most of the countries of Central and South America.

The low-prevalence areas comprise Australia, New Zealand, Northern and Western Europe, and North America.

In areas with a high prevalence the disease spreads in several ways: from mother to child during or immediately after childbirth, and through intensive bodily contact between young children and carriers. In areas with a low prevalence, transmission generally occurs through unprotected sexual contact with infected persons and/or the shared use of infected needles or other materials amongst intravenous drug users.[13]

3.5 Vaccines against the hepatitis B virus

3.5.1 Vaccine development

The first vaccine against hepatitis B became available in 1982. The antigen in that vaccine was purified hepatitis B surface antigen (HBsAg), isolated from carrier serum. Initially the vaccine was available only in limited quantities.[2]

In 1986 a vaccine became available that was comprised of recombinant HBsAg, manufactured in yeast cells using recombinant DNA techniques. This paved the way for cheap, large-scale vaccine production.[11]

Today there are monocomponent vaccines directed uniquely towards protection against hepatitis B and combined vaccines providing protection against both

hepatitis B and other diseases. The vaccines available on the Dutch or European market are depicted in the following tables.

Table 4 Monocomponent vaccines against hepatitis B available on the Dutch and/or European market. Sources: European Medicines Agency (EMEA) and the Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen or CBG).

Name	Composition (HBsAg dose)	Manufacturer	Dosage
Engerix-B (junior)	HepB (10µg/0.5ml)	GlaxoSmithKline	3-4x 0.5 ml (<16 years)
Engerix-B	HepB (20µg/1ml)	GlaxoSmithKline	2x 1ml (11-15 years); 3-4x 1ml (from 16 years)
HB-vax-DNA 10	HepB (10µg/1ml)	Merck, Sharp & Dohme	3x 0.5ml (<16 years), 3x 1ml (from 16 years)
HBVAXPRO 5	HepB (5µg/0.5ml)	Sanofi Pasteur MSD	3-4 x 0.5ml (<15 years)
HBVAXPRO 10	HepB (10µg/1ml)	Sanofi Pasteur MSD	3-4x 1ml (from 16 years)
HBVAXPRO 40	HepB (40µg/1ml)	Sanofi Pasteur MSD	3x 1ml (adult predialysis and dialysis patients)
Fendrix	HepB (20µg/0.5ml)	GlaxoSmithKline	4x 0.5ml (from 15 years, for patients with poor renal function, including (pre)hemodialysis patients)

HepB = Hepatitis B

Table 5 Hepatitis B combination vaccines available on the Dutch and / or European market. Sources: EMEA and CBG.

Name	Composition (HBsAg dose)	Manufacturer	Dosage
Procomvax	Hib-HepB (5µg/0.5ml)	Sanofi Pasteur MSD	3x 0.5ml (infants)
Twinrix paediatric	HepA-HepB (10µg/0.5ml)	GlaxoSmithKline	3x 0.5 ml (1 to 15 years)
Twinrix adult	HepA-HepB (20µg/1ml)	GlaxoSmithKline	3-4x (>16 years)
Ambirix	HepA-HepB (20µg/1ml)	GlaxoSmithKline	2x 1 ml (1 to 15 years)
Tritanrix HepB	DwPT-HepB (10µg/0.5ml)	GlaxoSmithKline	3x 0.5ml (infants)
Infanrix Penta	DaPT-polio-HepB (10µg/0.5ml)	GlaxoSmithKline	3-4x 0.5ml (infants younger than 36 months)
Infanrix Hexa	DaPT-polio-Hib-HepB (10µg/0.5ml)	GlaxoSmithKline	3-4x 0.5ml (infants younger than 36 months)
Quintanrix	DwPT-Hib-HepB (10µg/0.5ml)	GlaxoSmithKline	3-4x 0.5ml (children up to 1 year, booster from 2 years)

Hib = *Haemophilus influenzae* type b; HepB = Hepatitis B; HepA = Hepatitis A; D = Diphtheria; wP = whole cell pertussis, aP = acellular pertussis, T = Tetanus

3.6 The efficacy of vaccination

The protective action of hepatitis B vaccination is related directly to the development of antibodies after vaccination. An antibody level of more than 10 international units per litre (IU/l), measured one to three months after administration of the final dose, is regarded as a reliable marker of long-term protection against infection.[13,27,28]

A complete vaccination series generally comprises three or four injections. A few vaccines can be administered in two doses, given six months apart. This series yields protective antibody levels amongst more than 95 percent of children and young adults. The percentage drops with subject age: for those older than 40 it falls to 90 percent, and for those aged 60 it falls to 65 to 75 percent.

Premature and underweight newborn babies (<2,000 grammes) do not always react well to vaccination directly after birth; but when they are at least a month old they generally react well to vaccination, irrespective of birth weight or duration of pregnancy.[13]

The non-response of premature and underweight newborn babies can be a problem for the children of carriers, because their vaccination schedule involves a first dose within 48 hours of birth; for this reason a serological check is performed in this group as well, both for underweight and normal-weight babies.

The use of combined vaccines against diphtheria, whooping cough (pertussis), tetanus, polio, illness caused by *Haemophilus influenzae* type b (Hib), and hepatitis B seems to cause no problems for the efficacy of each vaccine. Antibodies against Hib do appear in lower concentrations after vaccination with combined vaccines compared with separate vaccines; however, functional immunity remains present.[29,30] The simultaneous use of hepatitis B vaccines with a vaccine against illness caused by pneumococci also appears to form no obstacle to the effectiveness of either. The absence of relevant interference has been demonstrated for the Engerix-B (HepB) and Infanrix hexa (DTaKP-Hib-HepB) vaccines, amongst others.[31-36]

As the vaccination of 12-year-old girls against cervical cancer caused by the human papilloma virus (HPV) is to be introduced in the Netherlands, it is important to find out whether this vaccine could be administered together with a hepatitis B vaccine. The European Public Assessment Reports (EPARs) of the European Medicines Agency (EMEA) indicate that no data is yet available on the combination of Cervarix™ (GlaxoSmithKline) with hepatitis B vaccine. The combination of Gardasil® (Sanofi Pasteur MSD) and Recombivax HB (Merck) has, however, been studied. Recombivax HB is marketed under this name in

America and Canada and is identical to the HBvaxPRO (Sanofi Pasteur MSD) used in the Netherlands. The study showed that the average level of hepatitis B antibodies was lower after using the combined vaccine, but that the difference was probably not clinically significant. More than 96 percent of those vaccinated still showed well above the level of 10IU/L of antibodies regarded as providing effective protection.[37,38]

As we have described, a hepatitis B vaccination is deemed to confer a protective effect if an antibody level of more than 10 IU/L is achieved, measured after administration of the last dose. For all the vaccines shown in Tables 4 and 5, their prescribed use yield these antibody levels in more than 95 percent of vaccinated children and young adults. In the opinion of the committee there are no relevant differences between the available monovalent and combined vaccines in terms of the protection they confer against hepatitis B.

3.7 The effectiveness of vaccination

Besides the *efficacy* as determined in experimental research and described in the last section, the *effectiveness* of vaccination is also important: to what extent does the vaccine confer protection under ordinary, everyday circumstances?

A relatively large amount of effectiveness data is available from Taiwan, where children have been vaccinated against hepatitis since 1984. Between 1984 and 1999, carrier prevalence fell from 9.8 percent to 0.7 percent.[39] Only 0.8 percent of a study group of children thereafter underwent asymptotic infection, and in not a single case did this turn into hepatitis B carrier status.[40] The incidence of liver cancer amongst children aged between 6 and 14 fell from 0.7 per 100,000 before vaccination was introduced (1981-1986) to 0.36 per 100,000 in the period 1990-1994, and liver cancer mortalities fell by 60-70 percent.[41] Mortalities resulting from fulminant hepatitis B, a life-threatening form of acute hepatitis, fell by about 70 percent.[42]

In assessing these figures it should be remembered that hepatitis B used to be very prevalent in Taiwan, and that the children were vaccinated using plasma vaccine and not today's recombinant vaccine.[43]

Research in Alaska and in the Gambia, two other countries in which hepatitis B used to be common, showed similar results.[44-46] In the Gambia, vaccine effectiveness was found to be 86.3 percent against infection and 92.3 percent against carrier status. Carrier status fell from 10 percent before the introduction of vaccination to 0.6 percent thereafter.[47]

Examples of the influence of hepatitis B vaccination in intermediate-endemic countries can be found in Malaysia and Italy. In Malaysia the seroprevalence of

carrier status amongst schoolchildren fell from 1.6 percent in 1997, before the introduction of the vaccination programme, to 0.3 percent in 2003. In Italy the incidence of acute hepatitis B fell from 11 per 100,000 in 1987 to 3 per 100,000 in 2000.[48] Other researchers reported that the incidence of acute hepatitis B fell from 12 per 100,000 before the vaccination programme to 1.5 per 100,000 in 2005. The reduction was greatest in the group aged between 15 and 24 years, in which incidence fell from 41 to 0.5 per 100,000. In this large-scale vaccination campaign, incidence was also strongly reduced amongst pubertal children and unvaccinated adults, which means that in this case a group immunity had been built up.[49]

The prevalence of carrier status in North America varies, from high in the north (Alaska) to low in the south. National surveillance data for acute hepatitis in the US indicated a 75 percent fall in new HBV infections in 2004 compared to 1990 (before the introduction of general vaccination). In the age groups which became eligible for general vaccination or catch-up vaccination this fall was even higher, at 94 percent, but amongst young adults (20 to 39 years of age) and adults (>40 years) falls of 74 percent and 30 percent respectively were reported in the incidence of acute hepatitis B.[50]

3.8 The duration of protection conferred by vaccination

As described earlier, an antibody titre of 10 IU/L, measured between one and three months after the last dose of a vaccine series, is regarded as a reliable marker of long-term protection. After intramuscular injection of the vaccine, the antigen comes into contact with the B and T lymphocytes in the local lymph glands. These lymphocytes then spread to other lymph glands, to the spleen and the bone marrow. The B lymphocytes become plasma cells and form IgG antibodies, the so-called ‘humoral reaction’. This antibody formation process can continue for years, and forms the basis for long-term protection.

Besides the protection offered by antibodies, there is also cellular defence. This is founded on the proliferation of T lymphocytes having a receptor for HBsAg. This cellular response removes infected cells and is essential for the body to be able to clear up an existing infection.[51]

Cellular immunity can still exist even when no antibodies can be seen. Specific memory T and B cells have been shown in people with less than 10 IU/L of antibodies in the blood.[52,53]

Functional immunity appears to be present more than 10 years after the primary vaccination.[54] If antibodies are no longer found in the blood, it is usually possible to use the subject’s immune memory to bring about a rapid immune

reaction by exposure to hepatitis B antigen, for instance a one-off repeat injection with hepatitis B vaccine.[55] A renewed exposure to the actual virus will probably have the same effect.

However, three recent research studies have reported the absence of such an antibody reaction amongst a proportion of children 15 years after their successful vaccination at birth.[56,57,58] It is uncertain whether the situation these reports describe is comparable with the Dutch hepatitis B vaccination programme and the combination vaccines it employs; all three of these research studies were carried out in high-endemic countries. It is also open to question whether the absence of such an immune memory response carries a risk, because none of the children had become chronically infected. In two of the studies the children had been given primary vaccinations which used a low dose of vaccine,[56,58] and in the third study low doses had been used for a large part of the primary vaccination series.[57] Here too there were children who later, as adolescents, did not react to a repeat injection of recombinant vaccine, but the study did not report what the doses of the original vaccine series had been or whether the primary vaccination had yielded an adequate response.

3.9 Passive protection

Apart from active immunisation, it is also possible to confer ‘passive protection’ by the direct administration of hepatitis B immunoglobulin (HBIg) antibodies. This confers a degree of protection after a pinprick wound, for instance. The injection must be given within 48 hours of the wound and confers protection from infection in about 80 percent of cases. Such HBIg protection lasts for a few weeks or months. For immediate protection HBIg is also given to the babies of HBsAg-positive mothers, in advance of the protection that is built up through a course of vaccination.[51]

3.10 An inventory of Western European countries having a high-risk group based vaccination policy

In Western Europe there are a number of countries besides the Netherlands which have a high-risk group based vaccination policy: Denmark, Finland, Iceland, Norway, Sweden and the UK. Ireland was another such country until September 2008, when it introduced general infant vaccination against hepatitis B.

To get a clear picture of whether general vaccination is being considered in countries currently maintaining a high-risk group based policy, for each of these countries the committee consulted with persons closely involved in that coun-

try's national immunisation programmes. These consultants are listed in Annex B.

Ireland

Ireland recently introduced general infant vaccination. Between 1997 and 2005 reports of hepatitis B cases increased, particularly as a result of the immigration of people from high-endemic areas. It was also felt that it would be difficult to identify and vaccinate those at greatest risk. In Ireland, too, sexual transmission is the principal route of HBV transmission. Moreover, it was considered that the number of new infections would be likely to rise as a result of growing international travel traffic, the immigration of people from high-endemic areas, the rising incidence of sexually transmitted diseases, and intravenous drug use.

Ireland therefore elected to implement the general vaccination of infants. Two factors contributed towards the choice to not vaccinate prepubertal children, even though this would deliver health benefits more quickly. Firstly, the general vaccination of infants was held to be more cost-effective than that of prepubertals. Secondly, the feasible vaccination rate amongst infants was considered higher than amongst prepubertals, and for the latter a new infrastructure would have to be created.[*,59,60]

United Kingdom

The British Medical Association (BMA) and researchers have recommended the introduction of general child vaccination against hepatitis B.[61] This recommendation has yet to be followed up.

Denmark

Denmark does not have full access to all members of its high-risk groups. However, disease incidence is low, including amongst homosexual men. In 2005 Denmark decided to maintain the high-risk group approach and not to switch to general vaccination.[**]

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* L. Thornton, written communication, 2008.

** S. Poulsen, written communication, 2008.

Finland

Finland's programme reach is also incomplete, but current incidence is extremely low now that the number of infections amongst intravenous drug users has fallen sharply. Finland does not intend to switch to general vaccination.*

Iceland

Iceland has no central vaccination registration system, so nothing can be said with certainty about the reach amongst high-risk groups. Neither is an administrative distinction drawn between acute and chronic infections, so it is difficult to monitor the effects of this policy. Iceland is not discussing any possible changes to this policy.**

Norway

In 2007 the Norwegian national public health institute advised testing all pregnant women for HBV infection and adding a number of groups to the country's high-risk group policy: the sexual partners of drug addicts, all prison detainees, people with an HIV infection, medical students, and rape victims. It also recommended the adoption of general vaccination, as difficulties were being experienced in reaching all those in the high-risk groups, and because general vaccination would not be much more expensive than the existing high-risk group policy. The Ministry of Health has not yet adopted this recommendation.***

Sweden

Sweden is finding it difficult to reach adults in the high-risk groups. An expert committee is currently examining whether general vaccination would be an appropriate response.****

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* T. Leino, written communication, 2008.
** T. Gudnason, written communication, 2008.
*** B. Feiring, written communication, 2008.
**** A. Tegnell, written communication, 2008.

3.11 Conclusion

Hepatitis B can have serious consequences

In rare cases acute hepatitis B can have fatal consequences. Chronic infection can result in serious long-term complications and in death from liver damage. In young children in particular, an infection is often asymptomatic and this raises the likelihood of the development of carrier status. The asymptomatic course of the disease means that incidence monitoring often suffers from under-reporting.

There are only limited treatment options for hepatitis B

There is at present no treatment for acute hepatitis B. The treatment of chronic hepatitis B with interferon or nucleoside/nucleotide analogues is not always successful, and such treatment has often to be administered for the rest of the patient's life. The options for the surgical remedy of serious liver damage are limited and costly, and such operations frequently fail to completely cure the patient.

Hepatitis B vaccination protects against infection and carrier status

The data presented in this chapter shows that hepatitis B vaccination confers a high degree of protection in terms of both efficacy (in research settings) and effectiveness (in actual practice). Vaccination protects against infection, carrier status, and the disorders that can follow, such as liver cancer. In large-scale vaccination programmes, even non-vaccinated persons benefit from the group immunity that arises.

Uncertainty exists about the duration of protection

It is not yet certain how long protection is conferred by vaccination. Experience with hepatitis B vaccines now covers a period of 26 years, and the protection conferred by these vaccines does not appear to have diminished or disappeared, but the possibility cannot be discounted. Certainly, after infant vaccination in low-prevalence areas, long-term protection – lasting several decades – is needed. Data on the long-term protection offered by combined vaccines is even more limited.

There are indications that interference exists between the components of combined vaccines, so it is not inconceivable that the protection offered by these vaccines against hepatitis B is of shorter duration. However, these indications arise from research into the antibody titres found years after vaccination. Functional immunity can still be present even when the antibody titre is low.

Countries with a directed policy have difficulties adequately reaching high-risk groups

Low-endemic countries generally have problems reaching everyone in their chosen high-risk groups. The situation in the Netherlands is relatively favourable, but here too, it is less than completely adequate (see Chapter 6). Several of these countries are considering the (additional) introduction of general vaccination. In Ireland this has now taken place. Norway is considering this step, while Sweden is still assessing whether the country needs general vaccination. Denmark has decided that the incidence of hepatitis B is so low that the existing, high-risk group only policy should be maintained.

Chapter 4

Criteria for the inclusion of vaccinations in the Dutch National Immunisation Programme

The introduction mentioned an assessment framework which employed seven inclusion criteria. This chapter will examine the context of these criteria, and how they can be used to assess the inclusion of proposed vaccinations, in more detail.

4.1 A single standard assessment framework for all vaccinations

In order to evaluate a vaccine's suitability for inclusion in the Dutch NIP, the advisory report *The Future of the National Immunisation Programme: towards a programme for all age groups* provides a standard assessment framework for vaccinations in the form of seven evaluation criteria.[4] Following this report, the Minister of VWS has determined that these criteria are to be the starting point in the assessment of vaccine inclusion in the NIP.

The seven inclusion criteria have been formulated with a view to the protection of the population as a whole, and to those groups for whom this protection is a priority. The criteria are formulated in an open manner, so that each criterion requires a thorough appraisal of the objective scientific literature and the arguments that arise from it.

4.2 Seven criteria

In the advisory report mentioned in the last section the Health Council describes the seven inclusion criteria and explains their use. These criteria provide a framework for the systematic discussion of arguments for and against the inclusion of specific vaccinations in the NIP.

The criteria are based on two ethical points of departure, namely (1) the optimal protection of the population as a whole and (2) the just distribution of this protection across groups within the population, such that those groups that need the most protection are afforded it.

The criteria are constructed hierarchically, that is to say that the evaluation of a subsequent criterion is only meaningful if the evaluation of the previous criterion has been positive. For instance, if the disease against which the vaccination offers protection occurs only infrequently or is not serious, then there is little point in going on to evaluate the effectiveness of a vaccine for it; and it only makes sense to weigh up the vaccine's cost-effectiveness if it has first been made clear that the vaccination is safe and effective for its target group.

The criteria do not constitute some sort of NIP 'vaccine inclusion form' that only needs to be filled in for the answer to simply roll out. The criteria demand that the available scientific knowledge be carefully and thoroughly considered before a pronouncement can be made. Moreover, judgements are seldom fully qualified: for instance, a vaccine is almost never fully effective or entirely without adverse side effects. The picture becomes even more complex when a number of options are being considered, each with its own strong points and weak points – as indeed is the case in the subject of this report, vaccination against hepatitis B.

The evaluation should be carried out by an independent, multidisciplinary body, such as the Health Council, which has no conflict of interests and which is not involved in the implementation of the vaccination programmes. The seven criteria are summarised in Table 6 below.

Table 6 Criteria for inclusion of a vaccination in a public programme (Source: Health Council, 2007)

Seriousness and extent of the disease burden

1 The infectious disease causes considerable disease burden within the population:
   - the infectious disease is serious for individuals, and:
   - the infectious disease affects or has the potential to affect a large number of people.

Effectiveness of the vaccination

2 The vaccination may be expected to considerably reduce the disease burden within the population:
   - the vaccine is effective for the prevention of disease or the reduction of its symptoms.
   - the necessary vaccination rate is attainable (if eradication of the disease or the creation of herd immunity is sought).

3 Any adverse reactions associated with vaccination are not sufficient to substantially diminish the public health benefit.

Acceptability of the vaccination

4 The inconvenience or discomfort that an individual may be expected to experience *in connection with his/her personal vaccination* is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.

5 The inconvenience or discomfort that an individual may be expected to experience *in connection with the vaccination programme as a whole* is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.

Efficiency of the vaccination

6 The ratio between the cost of vaccination and the associated health benefit compares favourably to the cost-benefit ratio associated with other means of reducing the relevant disease burden.

Prioritisation of the vaccination

7 The provision of vaccination may be expected to serve an urgent or potentially urgent public health need.

Chapter 5

Seriousness and extent of the disease burden

In order to establish the seriousness and scale of the disease burden (the first inclusion criterion), we must first assess how much illness and mortality is associated with the disorders brought about by infection with the hepatitis B virus. The assessment of the disease burden has a history: in the Netherlands, high-risk groups have been vaccinated against hepatitis B for over 20 years.

Infection with the hepatitis B virus can cause an acute illness (referred to as acute hepatitis B) and it can lead to chronic illnesses (referred to as chronic hepatitis B).

5.1 Illness and mortality from acute hepatitis B in the Netherlands

Compared with many countries in other parts of the world, hepatitis B occurs relatively infrequently in the Netherlands. As in other low-prevalence countries, such as the UK, Ireland, the Scandinavian countries and Finland, this has been the justification for pursuing the directed vaccination of high-risk groups rather than general vaccination.[62]

In assessing the disease burden we can make use of notification data, but this data suffers from under-reporting and under-diagnosis. Both recently acquired infections and chronic HBV infections can be asymptomatic, so infections can escape detection. This is particularly the case amongst children. Only 10 percent of children under the age of five show clinical symptoms after infection, compared with 30-50 percent of older children and adults. Infections which begin

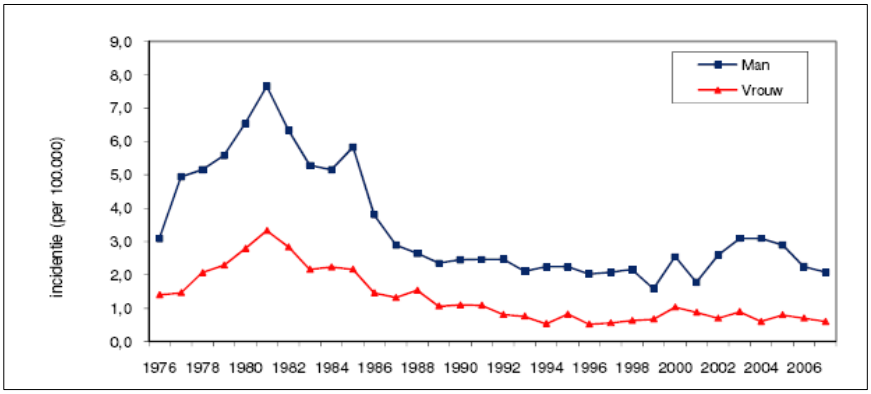

Figure 1 Reports of acute hepatitis B amongst males and females in the Netherlands, per 100,000 people per year. (Source: RIVM, 2008)

without apparent symptoms of the disease are the most likely to develop into chronic infections with serious health complications.

The number of such cases has always included more males than females (see Figure 1). In the early 1980s the total number of cases fell, which may have been linked to changes in sexual risk behaviour – whether or not in connection with the AIDS epidemic – and to preventive measures, including vaccination. Since about 1988 the number has remained more or less constant, with small fluctuations. Over the last ten years the number of reported cases of acute hepatitis B in the Netherlands lay between 1.4 and 2.0 per 100,000 persons per year.

In 2000 there was a rise amongst males, which was followed from 2003 by an approximately equal fall. This fluctuation is linked to changes in the numbers of men contracting an HBV infection through sexual contact with men.[63]

Between 2000 and 2006, according to data held by Statistic Netherlands (Centraal bureau voor de statistiek or CBS), an average of 3 people died every year as the result of an acute HBV infection.

5.1.1 *Age and sex distribution of acute hepatitis B patients in the Netherlands*

In general, males contract acute hepatitis B at an older age than do women. In men, acute hepatitis B occurs most frequently in the 35-44 age category. In women, it occurs most frequently in the 15-19 and 20-24 age categories.

In both males and females, reported incidence is low in the 0-14 age group. In the years 2003 to 2006 inclusive, there were 19 reports of acute hepatitis B in

this age group (an incidence of 0.16 per 100,000 per year).* As we have said, however, infection in young children is often asymptomatic, which means the infection is not immediately detected.

5.2 Illness and mortality from chronic hepatitis B in the Netherlands

The annual number of reports of chronic infections is stable, and in recent years has been a little under 9.0 per 100,000 people per year (see Table 7). It should be remembered that a chronic HBV infection is often long asymptomatic, and can therefore go unnoticed. The reported cases of chronic hepatitis B are separate from those of acute hepatitis B; they may arise from reports of symptomatic cases, cases found in the course of screening for pregnant women, and research into sources and contacts. The data on chronic hepatitis B does not, therefore, form a reliable measure of the incidence of new cases.

According to CBS data, the number of mortalities from chronic hepatitis B in the period 2000 to 2006 was 23 per year.[68] This number is probably subject to under-reporting to the CBS.

Table 7 Registered cases of chronic hepatitis B, absolute numbers and number per 100,000 people. (Source: RIVM, 2004-2007, n.k. = not known.)

	2003	2004	2005	2006
males	761 (9.2)	796 (9.8)	814 (10.1)	n.k. (n.k.)
females	721 (8.7)	668 (8.1)	629 (7.6)	n.k. (n.k.)
total	1,482 (8.9)	1,464 (8.9)	1,443 (8.8)	1,492 (n.k.)

Age and sex distribution of chronic hepatitis B patients in the Netherlands

The age distribution of chronic hepatitis B has shown little variation over time for both males and females. In males the number of reports per 100,000 people is highest in the 20-44 age group; in females the number is highest in the 20-34 age group.**

This age difference between males and females might be partly explained by the HBV screening given to pregnant women, which means that chronic hepatitis B is detected earlier in this group.[69]

* S.Hahné (RIVM), written communication, 2009.
** S. Hahné (RIVM), written communication, 2008.

5.3 Transmission patterns of acute and chronic hepatitis B in the Netherlands

The data given in Table 8a show that in the period from 2003 to 2006 inclusive unsafe sexual contact was the single most important risk factor for acute hepatitis B in the Netherlands: almost two-thirds of the cases were transmitted through sexual contact. In at least half of these cases transmission took place between homosexual or bisexual contact between men. They also show that for a significant proportion of the patients the transmission route is unknown: in over a quarter of the acute hepatitis B cases reported in the Netherlands, none of the known risk factors is reported.

There are no data of infections through horizontal transmission. The number of perinatal infections is low, as most of the children of carriers have been protected by vaccination (see Section 5.5).

Table 8b shows the suspected transmission routes in chronic hepatitis patients. These are only available in percentage terms, and not in absolute numbers. In the majority of cases it concerns the transmission of infection from mother to child, because young children are particularly susceptible to developing carrier status. 2003 is the only year for which data is available for all known transmission routes; for subsequent years only limited data are available.

Table 8a Risk factors for transmission in acute hepatitis B patients in the Netherlands, absolute numbers (percentages). (Source: RIVM, 2004-2007, n.k. = not known.)

acute hepatitis B				
transmission route	2003	2004	2005	2006
sexual contact	194 (60.8)	176 (60.1)	190 (63.5)	158 (65.7)
drug injection	7 (2.2)	3 (1.0)	0 (0)	1 (0.4)
professional incidents	7 (2.2)	7 (2.4)	4 (1.3)	4 (1.7)
perinatal	2 (0.6)	2 (0.7)	4 (1.3)	n.k.
other	19 (6.0)	30 (10.2)	21 (7.0)	18 (7.5)
unknown	90 (28.2)	75 (25.6)	80 (26.9)	59 (24.7)
total	319 (100)	293 (100)	299 (100)	240 (100)

Table 8b Risk factors for transmission in chronic hepatitis B patients in the Netherlands, in percentages. (Source: RIVM: 2004-2007, n.k. = not known.)

chronic hepatitis B				
transmission route	2003	2004	2005	2006
perinatal	72	71	71	n.k.
sexual	13	14	12	n.k.
drug injection	2	n.k.	n.k.	n.k.
professional incidents	2	n.k.	n.k.	n.k.
other	11	n.k.	n.k.	n.k.

5.4 Location distribution of infection: at home and abroad

Table 9 shows that most new infections leading to acute hepatitis B take place within the Netherlands. Chronic infections, however, are more frequently contracted abroad. The number of cases of chronic hepatitis B is chiefly determined by the immigration of carriers from countries in which hepatitis B is more highly prevalent.[67] Vaccination in the Netherlands cannot, of course, offer these people any protection. About 15 percent of these carriers turn out to have been infected within the Netherlands. Virus carriers form a potential source of viral transmission to other people.

Table 9 Data on the probable geographical location of infection in patients with either acute or chronic hepatitis B in the Netherlands, in percentages. (Source: RIVM, 2004-2007, n.k. = not known.)

acute hepatitis B	2003	2004	2005	2006
in the Netherlands	75	78	80	82
abroad	13	16	13	11
unknown	12	6	7	7

chronic hepatitis B	2003	2004	2005	2006
in the Netherlands	12	15	19	n.k.
abroad	76	75	69	n.k.
unknown	12	10	12	n.k.

5.5 HbsAg carrier status amongst pregnant women

Dutch national screening of all pregnant women in 1990 revealed that 4.4 per 1,000 were HBV carriers. For those who were not born in the Netherlands, prevalence was estimated at 25 per 1,000.[70] In 2003 a 0.4 percent prevalence of carrier status amongst pregnant women was reported.[71] In 2003 the Health Council estimated that about 1,000 children a year were born of HBsAg-positive mothers. Without vaccination, this would mean 300 new childhood infections and 270 childhood carriers every year. It was then estimated that a vaccination programme for the children of carriers would prevent about 200 infections and 180 cases of carrier status every year.[3]

5.6 Liver cirrhosis and liver cancer in chronic HBV infection

Carriers have a 25 to 37 times greater risk of developing liver cancer than do non-carriers.[17] Liver cancer appears about twice as frequently in men than in women. The Dutch Cancer Registry (Nederlandse Kanker Registratie or NKR) has no data available on the number of liver carcinomas consequent on hepatitis B.

Before 2003 an estimate was made of the incidence of Dutch cases of liver cancer having hepatitis B viral infection as their cause. Of 307 liver cancer cases, 72 (23.3 percent) were suspected of involvement with hepatitis B.[72]

5.7 Conclusion

An under-reported and insidious course of disease

The available data on the disease burden brought about by hepatitis B is subject to under-reporting, because in its early stages chronic infection and carriership of the virus often run an asymptomatic course. This creates the risk that health complications and the risk of further transmission are not detected in time. The paucity of data available on the burden of disease is also responsible for a distortion of the real scale of hepatitis B as a public health issue.

Hepatitis B causes a substantial disease burden

In a 2007 advisory report the Health Council evaluated the disease burden caused by hepatitis B in the Dutch population as being ‘substantial’. The arguments for

this were that acute hepatitis B can have serious consequences; that chronic infection carries a considerable risk of complications; and that carrier status forms a source for the further spread of the disease in the population. Taken together, the various subpopulations facing these risks form a substantially large group.

In this chapter, the evaluation of hepatitis B as a public health issue has been further substantiated. The incidence of the disease in the Dutch population is low compared to that in many countries in other parts of the world. Nevertheless, in this country between 200 and 300 cases of acute hepatitis B and about 1,500 cases of chronic hepatitis B are reported every year, as are a number of mortalities from acute hepatitis B and an average of 23 mortalities from chronic hepatitis B.

At the same time we must take account of considerable under-reporting. Especially for those infected perinatally or at a young age, the disease often develops asymptomatically and carrier status is the result. If carrier status develops, this can cause serious and permanent health damage and even death.

Although acute hepatitis B occurs with greatest frequency in specific high-risk groups, a quarter of all acute hepatitis B cases are not attributed to any known risk factor. Clearly, hepatitis B is less limited to specific high-risk groups than has been assumed up to now.

The number of cases of chronic hepatitis B is largely determined by the immigration of carriers from countries where hepatitis B is prevalent. Naturally, vaccination in the Netherlands does not confer protection to these people. However, about 15 percent of all carriers turn out to have been infected in the Netherlands. Virus carriers form a potential source for the spread of the disease to others.

The disease burden has not fallen, despite intensive directed programmes

After a fall in the 1980s, the disease burden caused by hepatitis B has since stayed more or less the same over time. The intensification of vaccination programmes directed towards high-risk groups has so far failed to yield any clear further fall in this disease burden. There is therefore cause to reconsider the adequacy of the current approach.

Chapter 6

The effectiveness of high-risk group vaccination in the Netherlands

In the last chapter, it was established that while hepatitis B does not appear frequently in the general population, it can have serious consequences for the individual, because of the risk of serious complications and the spread of the disease by carriers. This chapter will assess the effectiveness of the high-risk group vaccination programmes currently being employed in the Netherlands (inclusion criterion 2).

6.1 The vaccination of the infant children of HBsAg-positive mothers in the Netherlands

As was described in Section 2.2, in the Netherlands all pregnant women are offered a screening for HBV carrier status, at around the twelfth week of pregnancy. If a woman turns out to be a carrier, her newborn child is given specific hepatitis B antibodies and hepatitis B vaccine directly after birth.

This screening and vaccination programme has been subjected to operational evaluation on a number of occasions.[1,3,6,73] Each time the conclusions have been that the degree of coverage is incomplete and that the timeliness of the various vaccine dose administrations is less than perfect. RIVM report figures for the years 2006 to 2008 (children born in 2003-2005) show that the degree of vaccination in the children of mothers with carrier status has risen from 90.3 percent to 97.4 percent.[8]

Data on the actual effect of vaccination on the children of carriers is available for the years 2003-2005. In this period a different vaccination schedule was employed; besides being given hepatitis B antibodies as soon as possible after birth, the children were administered vaccine doses at the ages of two, four and eleven months. The city of Amsterdam, which used yet another vaccination schedule, is not represented in this data. Of the 1,105 children who were vaccinated according to this schedule, up to 10 percent turned out to be potentially inadequately protected; however, this led to only 8 breakthrough infections (0.7 percent). The longer the time interval between the third vaccination dose and the blood test, the greater the likelihood of an anti-HB titre below the required level. Amongst those children who were given serological checks within a year of the third vaccination dose, only 2 percent were potentially inadequately protected.[74,75] Since 2006, the midwife or gynaecologist who attended the birth is required to give the newborn baby a first dose of the vaccine as soon as possible after birth, at the same time as antibodies are also given to confer immediate protection.

Screening actually takes place amongst about 90 percent of the country's pregnant women.[76] In 2003 the Health Council estimated that about 1,000 children were born to HBsAg-positive mothers every year, resulting in 300 infections and 270 cases of carrier status in instances where no vaccine had been given. The screening and vaccination programme was seen as being potentially able to prevent about two-thirds of these infections and carrier status developments.[3]

The Health Council therefore looked into ways of improving the programme. In 2003 and 2007 it advised that a committee be appointed to closely supervise the programme in order to extend its effective reach.[3,4] In 2006, the Dutch Centre for Population Research (Centrum voor Bevolkingonderzoek or CvB) set up a Programme committee on Neonatal Screening (PNS) which advises the CvB directly on the national implementation of the programme. Even if the Netherlands elects to adopt general vaccination, this screening and immunisation programme will remain of crucial importance.

At the time, the Health Council wondered whether linking this programme to the NIP was desirable. The link arose because it was felt that this approach would achieve a high level of coverage, but more pragmatic reasons had also played a role: a separate GGD programme was not possible in all Dutch municipalities, as some did not have a functioning infectious diseases department. In 2003 the Council concluded that adapting the programme to the NIP had led to a number of undesirable compromises, including the postponement of vaccinations and a relatively low reach, and that bringing the programme into the NIP had introduced a risk that the very fact that this was a post-exposure prophylaxis – in

other words, the medical treatment of an existing condition – might be overlooked. In the Council's view, the programme's aims would probably be better served in some other way; the Amsterdam model, in which the children of carriers are vaccinated in a separate programme at the ages of 0, 1 and 6 months, offered a good example of the possibilities.[3] However, the Minister of VWS elected to adopt the Council's alternative proposal, namely to maintain the programme's links with the NIP.

6.2 The vaccination of patient groups

Little data is available on the effectiveness of vaccination against hepatitis B in patient groups. In 2000 it was reported, however, that the coverage level amongst haemodialysis patients, peritoneal dialysis patients, haemophilia patients and the mentally handicapped was above 90 percent.[7]

6.3 The vaccination of medical and paramedical staff

In 2000 it was reported that the vaccination coverage level amongst medical and paramedical staff varied strongly: amongst medical students it was 100 percent, while amongst hospital staff, dentists and thrombosis nursing staff it was 70-80 percent.[7] In 2006 it was reported that in hospitals, all persons who might form a risk had either been vaccinated or would be vaccinated.[77]

6.4 The vaccination of infant children of parents from intermediate and high-endemic countries

No effectiveness data is yet available on the programme which vaccinates children if at least one of their parents comes from a country in which hepatitis is relatively prevalent (more than 2 percent carrier status). After its introduction in 2003, the Health Council recommended that the programme be reviewed after three years.[1] This review would take pains to establish whether the programme methods had adequately reached its intended subpopulation. An effectiveness evaluation is difficult to perform as the programme involves a relatively small number of disease preventions. Moreover, any breakthrough infections are usually asymptomatic in young children. Nevertheless, the RIVM has an effectiveness evaluation planned for 2009.

The recent RIVM report on the vaccination coverage level in the Netherlands (mentioned in Section 6.1) does, however, provide an indication of the reach of this hepatitis B vaccination programme in children born between 2003 and 2005.

The percentage of children fully vaccinated against hepatitis B, where one or both of the parents came from a country where hepatitis is relatively prevalent, rose from 86.7 percent to 90.7 percent. The vaccination coverage level for DPT-polio-Hib turned out to be lower than average: about 94 percent were vaccinated. The difference in vaccination coverage level between the hepatitis B vaccination and the DPT-polio-Hib vaccination is explained by the fact that at that time separate vaccines were still being used; since the introduction of a pneumococcal vaccine in 2006, a combined DPT-polio-Hib-HepB vaccine has been employed. In this subpopulation, the average vaccination coverage level against DPT-polio-Hib and hepatitis B is lower than it is for the basic DPT-polio-Hib vaccinations in all infant children, namely over 96 percent. This is an indication that vaccination coverage levels amongst the children of immigrant parents is lower than those amongst the children of the indigenous Dutch.[8]

The selection of children for vaccination in this programme takes place in the following way. Children of whom both parents were born in a country with a prevalence of carrier status lower than 2 percent are given no hepatitis B vaccination; all other children *are*. In selecting the children who are not given this vaccination, use is made of a 'negative countries list' which is drawn up on the basis of WHO data on carrier prevalence. The use of this data introduces a certain arbitrariness, and this formed one of the reasons that the Health Council recommended a review be held three years after the introduction of the programme. The committee has received signals from the field that the selection process is, indeed, less than perfect. In cities where the subpopulation in question is large, this can obstruct the effectiveness of the programme.

6.5 The vaccination of people in behavioural high-risk groups

The RIVM has been evaluating the effectiveness of the vaccination of people from behavioural high-risk groups since the intensification programme which started in 2002.[64] Epidemiological data and blood samples are being collected from all reported acute hepatitis B patients. The spread of HBV types in high-risk groups is being analysed with the help of DNA typing.

It is not clear whether the intensification of vaccination in these groups has led to a fall in incidence. During the research period (2003-2007) the incidence of acute hepatitis B did fall – amongst males it fell from 3.1 to 2.1 per 100,000 and amongst females from 0.9 to 0.6 per 100,000 – but in the period immediately preceding this study the incidence had risen (see Figure 1 in Section 5.1), so the fall during the research period may simply have been part of a normal fluctuation.

Indications for an effect also emerge from the analysis of the data per high-risk group. The number of cases of acute hepatitis B in the largest high-risk group, that of homosexual men, fell from above 100 in the period 2003-2005 to about 80 in the period 2006-2007. The median age rose from 38 in 2004 to 42 in 2007; no similar rise in median age appeared in the other high-risk groups.

The genotyping made it clear that different HBV types are found in different high-risk groups. Six genotypes were found. Amongst homosexual men a single virus type, genotype A, was found to be the most common, with relatively little variation between different strains. Heterosexuals did not display such a clear majority of any single genotype, and there was a larger range of strains within each genotype. Clusters of related infections occurred with lower frequency than amongst homosexual men, and were smaller in scale. In many cases there was a link with a foreign country. This data could indicate that the spread of HBV infections amongst homosexual men in the Netherlands is common. Amongst heterosexuals, on the other hand, new introductions occur with greater frequency, including via carriers from countries where HBV has a high prevalence.[64]

Similar research was carried out earlier in Amsterdam, in a study which compared the period 1991-1997 (before the introduction of directed vaccination of behavioural high-risk groups) with the period 1998-2003. The study observed a reduction in the number of cases of acute hepatitis B amongst intravenous drug users and their heterosexual partners. However, there was also a fall in the size of the group itself, so this reduction was probably not caused by the vaccination programme. No fall in incidence levels was observed amongst homosexual men. Remarkably enough, there was a rise in the median age in this group: from 31 years in the first period, to 35 years in the second. It is not entirely clear how these findings are to be interpreted, but the researchers are of the opinion that since the incidence of acute hepatitis B remained stable despite indications for increased sexual risk behaviour, vaccination may well have prevented a rise in this incidence.[78]

An important finding of this research study is that an intensive campaign nevertheless failed to reach a large part of the behavioural high-risk groups in Amsterdam. Estimates of the vaccination coverage level varied from 12 percent (homosexual men) to 42 percent (heterosexuals with a variety of sexual partners). A substantial number of those in the high-risk groups is already infected and therefore no longer benefit from vaccination, but even allowing for this fact the researchers estimated that 48 percent to 72 percent of the members of behavioural high-risk groups in Amsterdam still run the risk of contracting hepatitis B.[78] Other research into homosexual men in Amsterdam reached similar conclusions; there a marginal reduction was observed in the incidence of acute hepatitis

B because of the low vaccination coverage level, the relatively short period in which the programme has so far been active (from 2002), and because of an increase in sexual risk behaviour. However, it was felt that vaccination had prevented a rise in incidence. The study urged the intensification of the programme, particularly amongst homosexual men with a high risk profile.[79]

In the Municipal Health Service regions of Rotterdam, Utrecht and Oostelijk Zuid-Limburg/Westelijke Mijnstreek, data have been collected on the degree to which people in behavioural high-risk groups – intravenous drug users, men with homosexual contacts and prostitutes – had been successfully reached by a programme for their vaccination, two years after its implementation. It showed that 44 percent of the drug users had been vaccinated, of which 67 percent had undergone a full series of three or more doses; 50 percent of homosexuals had been vaccinated, of whom 84 percent had completed the course; and 63 percent of the prostitutes had been vaccinated, of whom 79 percent in full.[80]

Finally, there is data from a national research study into the vaccination coverage level in behavioural groups over the period 2003-2007. This study provides estimates of the vaccination coverage level of 7 percent amongst homosexual men and 18 percent amongst heterosexuals with different partners. It also estimates that 30 percent to 81 percent of those in behavioural high-risk groups is at risk of contracting hepatitis B.* Using questionnaires, the Dutch Schorer institute for homosexuality, health and welfare has also done research into protection against hepatitis B in homosexual men. Its 2008 monitor reports that 48 percent are fully vaccinated against hepatitis B and 10 percent incompletely.[81]

6.6 Conclusion

The prevention of mother-to-child transmission remains essential

Preventing the transmission of the hepatitis B virus from mother to child is a cornerstone of the fight against hepatitis B in the Netherlands; since 1989 the country has had a programme for screening pregnant women and vaccinating their newborn children if the mother is found to be a carrier. This programme prevents a great deal of illness, but its reach is incomplete. The programme remains of crucial importance even if general vaccination is introduced.

* Written communication, R. van Houdt, 2008.

The vaccination of patient groups and (para)medical staff is now a success

The vaccination coverage level amongst patient groups is over 90 percent. There are also indications that high-risk groups amongst hospital staff have already been, or will be, vaccinated.

The limits of the behavioural high-risk group approach appear to have been reached

The behavioural high-risk group based approach has achieved a great deal. The range of high-risk group vaccination programmes has been expanded, particularly for behavioural high-risk groups. However, despite this large-scale intensification the programmes still have an incomplete reach and there are only limited indications of reductions in illness incidence. It is possible that these will be revealed after a few more years have passed.

Programme reach amongst the infant children of parents from intermediate and high-endemic countries should be reviewed

This programme is of great importance because of the risk of infection at a young age and the associated high risk of developing carrier status and its long-term health sequelae. There are indications that the vaccination coverage level in this group could be improved; this would therefore improve programme reach. A review of the programme's effectiveness is in preparation for 2009.

General vaccination should be reconsidered

The recommendation to vaccinate the infant children of parents from intermediate to high-endemic countries arose from a request to the Health Council for advice on the desirability of general vaccination. At the time the advisory report was published (2001), the vaccination of all children against hepatitis B was not considered expedient. It was recommended to compare the effectiveness of a programme which included general vaccination with a programme which approached only the high-risk groups. This comparison, for which model research is required, has become even more important now that the limits of the high-risk group based approach appear to have been reached. The results of this model comparison are now available, and will be discussed in Chapter 9.

Chapter 7

Vaccination safety

It is very important that the vaccines used in the NIP are safe (inclusion criterion three), and for any vaccine used against hepatitis B it is important that any adverse health effects do not detract from the health benefits accruing to the individual and to the population as a whole. Hepatitis B vaccines have long been extensively employed in a variety of countries, so we have access to considerable practical experience of their effects.

7.1 The classification of adverse side effects

The severity of adverse side effects is not always assessed according to the same classification system, and this means that research studies into such side effects can display considerable variability between data reports. In its advisory report *The future of the National Immunisation Programme: towards a programme for all age groups* the committee clarifies its classification of the severity of adverse side effects. The concept of 'severe side effect' was defined as follows: death, serious neurological symptoms, or permanent bodily impairment. Another category was defined for 'extremely aggravating side effects': side effects which, while they had no permanent bodily consequences, nevertheless represented a serious problem for the child and its parents and could lead to profound anxiety: convulsions, collapses, and persistent screaming and crying. Finally, all adverse side effects that did not belong in either of the first two categories were classified as 'other side effects': this included fever, malaise, loss of appetite, drowsiness

and lethargy, and reactions in the location of the injection site such as pain, swelling or redness.[4]

7.2 The safety of infant hepatitis B vaccination

Vaccines admitted to the European market are first scientifically evaluated for efficacy and safety by the Medicines Evaluation Board (*College ter Beoordeling van Geneesmiddelen* or *CBG*) and the EMEA. This has applied both to separate hepatitis B vaccines and to combined vaccines comprising a hepatitis B component. However, the large-scale use of vaccines in public programmes involves separate safety requirements, and safety issues are therefore tested against a separate criterion.

The use of combined hepatitis B vaccines in infant children is associated with generally mild and transient adverse side effects: pain, redness and swelling at the injection site, tiredness, headache, nausea, rash, fever and dizziness.[82,83] These generally fall into the category of 'other side effects' according to the committee's definition described in the last section. The frequency of these mild side effects varies considerably in a number of post-marketing research studies (see Table 10).

The European Public Assessment Report (EPAR) of a DPT-polio-Hib-HepB combined vaccine reports that reactogenicity following primary vaccination was comparable with that of DPT-polio vaccines. High fever (≥39.5°C) was more common after a booster vaccination than it was after the primary series.[29] These observations are confirmed in post-marketing research which found that 1.7-5.4 percent of those vaccinated developed high fever after their booster vaccination in the second year of life, compared to the 0-1.4 percent who developed such a fever after primary vaccination as infants.[32,33]

Table 10 Frequency of adverse reactions after primary vaccination with a combined vaccine comprising a hepatitis B component. (Sources: see references [32,33,84-91])

Pain/soreness at the injection site	14.3-24%
Redness	13-43%
Swelling	10.3-36.9%
Fever ≥38°C / ≥39.5°C	11-29.3% / 0-1.4%
Restlessness/crying	14.4-39.7%
Reduced appetite	0.6-28.5%
Tiredness	0.9-39%
Dizziness	17.5-31.6%

Clinical research and post-marketing research have shown that severe side effects – defined by the committee as death, serious neurological symptoms, or permanent bodily impairment – are very rare. It appears that serious illness following vaccination is seldom if ever the result of the vaccination itself.[92,93,86,32,87,90,94] The EPARs of hepatitis B vaccines also point to the fact that when serious disorders follow vaccination, only sporadically is a link found with the vaccination itself.[95,96]

The simultaneous use of separate vaccines against hepatitis B, infections caused by pneumococci or by meningococci C appears to have no detrimental effect on safety, no more than does the use of combined vaccines against diphtheria, whooping cough, tetanus, polio, invasive infections by *Haemophilus influenzae* type b, and hepatitis B. Adverse side effects appear no more frequently than when these vaccines are administered separately.[31-33,87]

7.3 The safety of prepubertal hepatitis B vaccination

The vaccination of prepubertal children generally makes use of separate hepatitis B vaccines. Here, too, the adverse side effects seen are generally mild and transient in nature. Such side effects are seen in about 3 percent of vaccinated prepubertals: these effects include pain at the injection site, rash, and tissue hardening. Not one of the available studies reports a single severe disorder as a result of vaccination.[97-99]

The vaccination of prepubertals, particularly girls, presents the possibility of the simultaneous administration of vaccination against cervical cancer. Research has been carried out into the simultaneous use of Gardasil (Sanofi Pasteur MSD) and Recombivax HB (Merck, identical to the HBvaxPRO that has been brought onto the European market). In a research study of 1871 women between the ages of 16 and 23, no serious side effects were observed in a seven-month follow-up period, and the pattern of side effects was identical to that of the separate administration of each vaccine.[37,38] No such data is yet available for Cervarix (GSK).

7.4 Hepatitis B vaccination and the risk of multiple sclerosis

In 2004 a study was published by Hernán and his colleagues in the scientific journal *Neurology*, which reported finding a statistically significant link between vaccination with recombinant hepatitis B vaccine and an increased risk of multiple sclerosis (MS).[100] This study had used adult patient data taken from the General Practice Research Database (GPRD), a digital database containing anonymised medical information from the UK's primary health care system.

Rumours of a possible link between hepatitis B vaccination and MS had been circulating for some time, particularly in France. A number of research studies have since searched for this link. In an advisory report published in 2001 the Health Council reviewed the available scientific literature on the subject and concluded that there were no indications of a causal link.[1]

The research carried out by Hernán was well designed and executed, better than many earlier studies. For this reason the committee has carried out a new evaluation of possible links between hepatitis B vaccination and MS, and of the implications for vaccination programmes against hepatitis B. The results of this assessment are given in Annex C.

Design and execution of the research study

The committee has assessed the evidential value of Hernán's research study and has concluded that it is unlikely that its findings can be explained by shortcomings in its design or execution. However, it concerns observational research that as such cannot furnish proof for a causal link between hepatitis B vaccination and MS, because it is impossible to remove every possibility of epidemiological bias.

Pooled research

In order to better compare the research work done by Hernán and his colleagues with the results of other research studies, the Health Council commissioned a systematic review of the epidemiological research that has been carried out into the link between hepatitis B vaccination and MS. This systematic review is given in Annex D. The pooled research gives no indications for a link between hepatitis B vaccination and MS.

The plausibility of a causal link

The committee has reflected on whether a plausible explanation can be given for the posited causal link between hepatitis B vaccination and the subsequent onset of multiple sclerosis. The scientific literature has suggested that identical amino acid sequences appear in an enzyme of the hepatitis B virus (Hepatitis B virus polymerase, or HB-pol) and in the myelin sheath of nerve fibres. It is conceivable that molecular mimicry could induce an autoimmune process in susceptible persons.

However, HB-pol forms no part of the recombinant vaccine; at most, it might appear in the form of a trace contamination. It is therefore extremely unlikely that the vaccine would provoke an autoimmune reaction. HB-pol does form part of the hepatitis B virus itself, and is found in relatively high concentrations in persons with an active HBV infection. In countries like the United Kingdom (and the Netherlands), it is precisely those people who run a higher risk of infection who are selected for vaccination. In these countries, it is vaccinated people who run the greatest risk of coming into contact with the virus and becoming infected. This might explain the statistical link between vaccination and MS found by Hernán. The link would then actually be between infection with the hepatitis B virus and MS. The apparent link with vaccination would arise because precisely those people running the greatest risk of catching the disease would be selected for vaccination against it: this problem is known as 'confounding by indication'.

In the committee's opinion, molecular mimicry does not form a logical causal explanation for a posited link between hepatitis B vaccination and MS. It does, however, form a possible alternative explanation for the findings of Hernán and his colleagues.

Follow-up research

While Hernán's research was still being evaluated, the results of a similar study of children was published; this had been carried out by Mikaeloff and colleagues in France as a follow-up to Hernán's work. As with Hernán this was a case-control study, in which the vaccination anamnesis was compared in 143 MS patients and 1,122 control subjects who did not have MS; however, in contrast to Hernán's study, this concerned children younger than 16 years of age. MS patients were taken from the KIDSEP cohort* that includes most incident cases of patients with childhood-onset MS in France. The control subjects were taken from a random sample of the general population and were matched by age, sex and geographic location.

Mikaeloff and his colleagues took as their starting point patients who had been diagnosed as having MS using objective criteria. As in Hernán's study, they based their data on exposure to vaccination on pre-prepared and collated sources, in this case vaccination booklets. The analysis of the data used much the same statistical techniques as had been employed by Hernán. However, not one of these analyses found indications for a link between hepatitis B vaccination and MS.[101]

* Kid Sclérose en Plaques.

One difference between Mikaeloff's research and Hernán's is that it concerned children. In contrast to the participants in Hernán's study, those in Mikaeloff's did not form members of a high-risk group for HBV infection. The risk of confounding by indication is therefore probably much smaller in Mikaeloff's research than it is in Hernán's. This might explain why Mikaeloff found no correlation and Hernán apparently did.

Mikaeloff and colleagues recently carried out a follow-up research study using the same cohort of children with MS and control subjects. Again, this found no overall correlation between vaccination and MS. However, if the analysis was limited to children who had duly received their childhood vaccinations in full – which was defined as having received at least one dose of BCG vaccine (Bacille Calmette-Guérin, against tuberculosis), a dose of MMR vaccine (against mumps, measles and rubella) and four doses of DTP vaccine – then a barely significant correlation was found with one particular hepatitis B vaccine.

However, the research study worked with several subgroup analyses and it is likely that this correlation is therefore the result of chance.[102]

The opinion of the committee

In the opinion of the committee, Mikaeloff's first research study is characterised by the same careful design and analysis as that of Hernán. It has the advantage of having children as its subjects. The research finds no indications of a link between vaccination using recombinant hepatitis B vaccine and MS. The findings of Mikaeloff's second study are probably the result of chance. On the basis of all the available data, the committee concludes that a link between vaccination using recombinant hepatitis B vaccine and the onset of MS is most unlikely.

7.5 Conclusion

Hepatitis B vaccination is safe for both high-risk group approaches and general vaccination

The safety of the vaccines used in the NIP is of great importance. After many years of experience with the vaccines, the available data on the adverse side effects of hepatitis B vaccination shows that vaccination against hepatitis B is safe. The frequency of side effects is low; the side effects that do occur are almost always of a mild and transient nature. The side effects do not detract from the health benefits obtained.

On the basis of an analysis of all the available data, the committee concludes that a link between vaccination with recombinant hepatitis B vaccine and MS is most unlikely. The committee concludes that vaccination against hepatitis B is safe when administered to persons with a raised risk of HBV infection, such as the children of mothers who are carriers, children with at least one parent from a country where hepatitis is endemic, and people from behaviour-linked high-risk groups. In the committee's opinion, the safety profile forms no impediment to the vaccination of all infant or prepubertal children against hepatitis B within the framework of a general vaccination programme. In these cases, too, vaccination against hepatitis B is safe.

Chapter 8

The acceptability of vaccination

The acceptability of a vaccination is also of great importance to the success of any given vaccination programme. The acceptability criteria are used to test whether the burden of vaccination for the individual bears a reasonable relationship to the health benefits for that person and for the population as a whole. The relationship between burden and health benefit is separately evaluated for the vaccination concerned (inclusion criterion four) and for the entire vaccination programme including the vaccination under consideration (inclusion criterion five).

The first acceptability aspect to consider is the question of the burden of vaccination for the person receiving it. The most visible effects of the vaccination are the discomforts with which it is associated, such as the stress of undergoing injection and the number of injections involved. Seen objectively these are perhaps minor discomforts, but the fact that they are experienced by a great many children means that they need to be given due consideration. It is the aim, after all, to make this burden as light as possible.

On the basis of the ‘acceptability within the vaccination programme as a whole’ inclusion criterion, the Health Council had earlier stated that under normal circumstances it wished to adhere to a maximum of two injections per session. This is not only important for the children involved and their parents; it is also important to keep the willingness to take part in the NIP as high as possible, so that the highest possible rate of vaccination coverage is achieved. This maximum of two injections per session is based on expert opinion and feedback from

the field, as there is little scientific data on this subject on which to base or reject an opinion.

Another aspect is the justice of the distribution of burdens and benefits between different groups. Problems might arise if the burdens of vaccination were systematically accorded to one group and the benefits always accrued to another.

8.1 The acceptability of vaccination against hepatitis B per se

8.1.1 In high-risk groups

Vaccination against hepatitis B currently concerns the groups described in Chapter 2, which discussed the design of the vaccination programme against hepatitis B. The health benefits accruing to these groups are high because of the groups' high risk of infection. For almost everyone in these high-risk groups, a hepatitis B vaccination involves additional injections alongside the regular NIP. However, it only amounts to three sessions with one injection per session; in the committee's opinion this burden is certainly reasonable when seen in relation to its health benefits.

For infants with at least one parent from a country where hepatitis B is relatively prevalent, and for Down's syndrome children, hepatitis B vaccination involves no additional injections, since use is currently made of a DPT-polio-Hib-HepB combined vaccine for these children. With the exception of the injection directly after birth, the same applies to the children of carriers. This, too, cannot be seen as a problem as the importance of vaccination is much greater.

8.1.2 In general vaccination

As in a number of other north-west European countries, the Netherlands has so far elected to adopt directed vaccination for people in high-risk groups. If this enables the effective prevention of hepatitis B, then this directed approach is to be preferred. The aim of the directed approach is to protect those groups for whom such protection is most urgent and at the same time to minimise the number of people who are given the vaccination even though they have no direct need for it. If these aims are met, then the directed approach can also make an important contribution towards the retention and expansion of public support for general vaccination.

However, it is important to know whether these aims are actually met in practice. The data presented in Chapter 6 shows that high-risk group directed pro-

grammes do not have an ideal reach. The results of model analyses carried out to compare the effectiveness of the high-risk group based approach and that of general vaccination (see Chapter 9) have suggested that general vaccination could achieve an important additional health benefit in the population as a whole. Evidently, those groups for whom protection is most urgent are also better reached by means of general vaccination.

In evaluating the acceptability of general vaccination, we have drawn a distinction between the ages at which this vaccination is administered: amongst infant children or prepubertal children. This evaluation weighs the burden of vaccination against its individual and collective importance.

At an infant age the individual benefit of vaccination is, with the exception of infants in high-risk groups that are already being vaccinated, impossible to assess in terms of potential risk behaviour. In later years, behavioural risk makes this individual benefit self-evident, but this cannot be said for the population as a whole. Nevertheless, individual risk is by no means straightforward to estimate using risk factors: it turns out that in about a quarter of all cases of acute hepatitis B in the Netherlands, none of the known risk factors is reported.

In assessing the collective benefit of vaccination, it must be taken into account that – as we have described – general vaccination can probably achieve additional health benefits in the population as a whole. For this to be the case, children must also be vaccinated who run no direct risk of infection. In vaccinating at infant age, no additional vaccination burden is involved if a DPT-polio-Hib-HepB combined vaccine is used; the infant continues to receive no more than two injections per contact session.

Given the lack of any additional injection burden, and the collective benefit it offers, the committee is of the opinion that the general vaccination of infant children is acceptable.

It is also possible to vaccinate at the ages of 0, 1 and 6 months using a separate vaccine. However, this involves an additional injection burden and requires three extra contact moments within the NIP. The committee judges this scenario to be unacceptable.

The vaccination of prepubertal children involves similar considerations. Here, too, general vaccination can be expected to bring substantial additional health benefits.

At this time the NIP does not vaccinate prepubertal children; the final set of NIP vaccinations, against DTP and MMR, are given at nine years of age. This means that two or three additional contact moments would have to be introduced. In contrast to the situation just described for the vaccination of infant children, here extra injections are necessary.

For most people in the Netherlands the risk of HBV infection appears during puberty. The general vaccination of prepubertal children therefore has the advantage of providing vaccination at an age closer to that at which the general population of the Netherlands runs the greatest risk of HBV infection.

Vaccination at this age has another potential advantage. There remains a certain degree of uncertainty about the long-term protection against hepatitis B that is conferred by vaccination. By administering vaccination against hepatitis B shortly before the age at which most people are exposed to risks of its infection, it is arguable that this provides longer effective protection. Given the limited additional injection burden, and the collective benefits it confers, the committee is of the opinion that the general vaccination of prepubertal children is also acceptable.

8.2 The acceptability of vaccination against hepatitis B within the National Immunisation Programme

8.2.1 In high-risk groups

For the most part, vaccination against hepatitis B in high-risk groups is organised in separate programmes, so there is no question of potential conflicts with other vaccination programmes within the NIP.

Vaccination organisations that form part of the NIP use the DPT-polio-Hib-HepB combined vaccine. This is the case for the vaccination of infants with at least one parent from a country where hepatitis B is relatively prevalent, children with Down's Syndrome, and the infant children of carriers. Here, too, the question of acceptability within the NIP forms no impediment.

8.2.2 In general vaccination

In the general vaccination of infants, the total injection burden – two injections per vaccination moment – can remain the same when use is made of a DPT-polio-Hib-HepB combined vaccine. There is then no question of potential conflicts with other vaccination programmes carried out within the NIP. From the perspective of its acceptability within the NIP, the committee therefore sees no impediment to the general vaccination of infants against hepatitis B. While the 0, 1 and 6 months schedule using a separate vaccine does not conflict with other vaccinations given within the NIP, this programme means that three extra contact moments have to be arranged, and it also imposes an extra injection burden. The committee judges this to be unacceptable.

The vaccination of prepubertal children is equally free of potential conflict with other NIP vaccinations. In the Netherlands, no other vaccines are currently given at this age.

The Health Council recently advised that the NIP should include vaccination against cervical cancer for girls.[103] It was recommended that for this purpose general vaccination be introduced for girls at the age of 12. This recommendation is due to be adopted in 2009. If the general vaccination of prepubertal children against hepatitis B were to be introduced, then it would be advisable to administer both these vaccines simultaneously; this would keep the number of vaccination moments to a minimum. In prepubertal children, a complete series of vaccinations against hepatitis B require two or three injections. A series of vaccinations against cervical cancer requires three injections.

If it were decided to introduce vaccination against hepatitis B alongside vaccination for cervical cancer, then boys would receive one injection and girls two injections at each vaccination moment. The committee sees no impediment to the general vaccination of prepubertal children against hepatitis B from the perspective of its acceptability within the NIP.

8.3 General vaccination means better protection for the whole population, including high-risk groups

In a public programme like the NIP the emphasis is on collective protection. In the case of vaccination against hepatitis B, the protection of the individual is a less prominent issue because of the relatively low risk, in general, of being infected. The committee notes that general vaccination protects not only those who fall outside the well-known high-risk groups, but also those within an important high-risk group which considerable efforts have so far failed to yield an adequate reach: homosexual men. Incidence of the disease is higher in this group than in the general population. Protection here serves a collective interest, because it is impossible to know in advance which people are going to belong to this high-risk group in the future. The committee sees another argument for general vaccination in the fact that no known risk factor can be cited in a quarter of the notified cases of acute hepatitis B. At least part of the people in this group will not, therefore, be reached by a high-risk group based policy.

8.4 Conclusion

Within the framework of the acceptability of vaccination, a high-risk group based approach is to be preferred when this is demonstrably effective

As is the case in a number of other north-western European countries, the Netherlands has so far elected to employ the directed vaccination of high-risk groups. When it enables the effective prevention of hepatitis B, this approach is the most acceptable. The aim of the directed approach is to protect those groups for whom such protection is the most urgent and at the same time to keep to a minimum the number of people who are given a vaccination of which they are in no direct need. If this aim is achieved, the directed approach can also make an important contribution to the retention and expansion of support for public vaccination.

The collective interest is served by general vaccination

Model analyses (see Chapter 9) which compared the effectiveness of the high-risk group approach and general vaccination concluded that general vaccination enables an important additional health benefit to be achieved in the population as a whole. It is also expected that those groups for whom protection is most urgent would be better reached by means of a general vaccination programme.

General vaccination against hepatitis B can be achieved at infant age by making use of a combined vaccine. This makes it possible to introduce general vaccination without subjecting those participating in the NIP to any additional injections.

Given the absence of an additional injection burden, and given the public interest, the committee is of the opinion that the general vaccination of infant children against hepatitis B, using a combined vaccine, is acceptable.

The vaccination of prepubertal children forms a possible alternative for the general vaccination of infants. This does require extra injections and new injection moments. However, the burden posed by these is limited and, in the judgement of the committee, acceptable.

General vaccination is acceptable within the National Immunisation Programme

An important consideration is the minimisation of the burden of vaccination for NIP participants. In the general vaccination of infant children, the injection bur-

den can stay the same – two injections per session – if use is made of a DPT-polio-Hib-HepB combined vaccine. In this case there is no question of potential conflicts with other NIP vaccinations. For this reason, the committee sees no impediment to the introduction of general vaccination of infant children against hepatitis B from the perspective of its acceptability within the NIP, provided use is made of a DPT-polio-Hib-HepB combined vaccine.

The committee also sees no impediment to the introduction of possible general vaccination of prepubertal children against hepatitis B from the perspective of its acceptability within the NIP.

If it is decided to introduce the general vaccination of prepubertal children, the committee advises that this be administered simultaneously with the vaccination of girls against cervical cancer, a matter on which the Health Council has recently advised.

Chapter 9

The efficiency of vaccination

The evaluation of inclusion criterion six, the efficiency of vaccination, means assessing the expected health effects, costs, and benefits of vaccination against hepatitis B. To this end, models have been developed which combine data on the epidemiology, disease burden and mortality of hepatitis B, its treatment, the efficacy and effectiveness of vaccination against it, and lastly the costs of this vaccination. The inclusion of general infant or prepubertal vaccination in the NIP is then compared with the current situation: vaccinating only people in high-risk groups. The influence of intervention strategies is expressed in the number of Quality Adjusted Life Years (QALYs) that a strategy might yield, and what these cost compared with the previous situation (no intervention, or a different intervention strategy). Expressing intervention effects in QALYs makes it possible, up to a point, to make comparisons between different interventions. In the Netherlands a preventive programme is generally deemed to be cost-effective when its costs are less than 20,000 euro per QALY gained.

9.1 Modelling different vaccination strategies

Previous modelling

The RIVM carried out an economic evaluation in support of the Health Council's 2001 advisory report *Universal vaccination against hepatitis B*.[1] Its analyses showed that the prevention of a relatively small number of carrier cases amongst

children who were in contact with carriers was of decisive importance in determining whether it was efficient to vaccinate as yet uninfected children having a raised risk of HBV infection.[1] This finding arose chiefly from the young age at which these children could become infected, the relatively large number that develop carrier status as a result, and the considerable individual and social costs that carrier status of the hepatitis B virus entail. About 90 percent of HBV-infected newborns develop carrier status. The older a person is, the lower the likelihood they will develop carrier status (see Table 3 in Section 3.2). In the analysis, the incremental cost-effectiveness ratio (ICER) depended on the discount rate (depreciation), the cost of the vaccine, and the prevalence of carrier status amongst immigrants.

Additions to the model

Since the RIVM report was published in 2000 this model has been expanded.[7] For instance, horizontal transmission has been included as a third transmission route alongside vertical and sexual transmission. The current model has incorporated new estimates for prevalence in immigrant populations. It has also introduced 'quality of life estimates' to enable the calculation of QALYs. The fall in the price of the vaccine has also had a favourable effect on the cost-effectiveness ratio. The discount rate for health effects has also been adjusted; in line with Dutch guidelines it has been set at 1.5 percent, in contrast to the 4 percent employed in earlier calculations.[104] The new discount rate has been employed in all the data presented in this chapter. In the most recent analysis, the cost-effectiveness ratio of a variety of risk group approaches is compared with possible general vaccination scenarios. Supplementary calculations have been carried out to derive the effects and costs of a catch-up vaccination for 12-year-olds, besides general infant vaccination.

Model design and uncertainties

In the dynamic transmission model that was employed, the model population was structured according to gender (male, female), age (between 0 and 60 years; it was assumed that after the age of 60 no transmission of HBV takes place) and sexual activity (six classes of activity).[105,106] For detailed information on the design of this model and its parameters, the reader is referred to an annex in a recent publication on this model.[106]

It was assumed that the male-female ratio was one to one. It was also assumed that the number of births is identical to the number of deaths, so the

population size of the model stays the same. In the model people are born, become sexually active at 15 years of age, enter one of the six sexual activity classes, and stay there all their lives. Each sexual activity class is associated with a certain degree of sexual activity, defined as the degree of partner change.

The scale of the six sexual activity classes in the model population reflected observed patterns of the actual frequency of partner change; large groups have relatively few new sex partners, while small groups have many new sex partners. The heterosexual and homosexual populations are modelled separately, and the two groups have no sexual interaction with each other. An important model difference between homosexuals and heterosexuals lies in the parameter values describing the degree of sexual activity.[106]

The simulation is run for a period of 50 years, the underlying assumption being that vaccination affords lifelong protection.

The natural course of a hepatitis B infection was modelled using an age-specific Markov model; the likelihood of becoming a carrier after infection is age-dependent. A recently infected person can, after a period which may be symptomatic or asymptomatic, either become immune or become a virus carrier. A distinction is drawn between carriers with active viral replication and those without. The likelihood of going on to develop the long-term sequelae of hepatitis B, such as compensated or decompensated liver cirrhosis and liver cancer, depends on whether the carrier has active viral replication or not. The number of mortalities prevented was corrected for deaths from causes other than hepatitis B. The deaths brought about by hepatitis B comprised cases of acute fulminant hepatitis B, compensated cirrhosis, decompensated cirrhosis, and liver cancer.*

In the model people could become infected by three means: by sexual contact, by mother-child transmission at childbirth (vertical transmission) and by domestic contacts between carriers and children (horizontal transmission). Infected people passed through the following stages: a latent phase in which the person was not yet contagious; an acute phase in which the person was contagious; and then a phase in which the person was either a virus carrier or had formed immunity. Vaccination brought a person into the vaccinated class.

Earlier analyses had used prevalence data taken from the PIENTER research study, which found a 0.2 percent prevalence of hepatitis B surface antigen (HBsAg), or carrier status, in the general population.[107] However, immigrants and people from high-risk groups were found to have been under-represented, so that this prevalence figure is probably an underestimate.

* A. de Wit, M. Kretzschmar (RIVM), written communication, 2008.

The model therefore used another approach. In order to approximate the prevalence of carrier status in the general population, three epidemiological scenarios were elaborated, on the basis of data in the literature on carrier prevalence amongst immigrants in their country of origin and recent Dutch statistics on immigration from a variety of countries of origin. This yielded an estimated carrier prevalence amongst immigrants of 2.15 percent in the lowest scenario, 3.47 percent in the intermediate scenario, and 4.70 percent in the highest scenario.[106] Because the immigrant population is also proportionally distributed across the six sexual activity classes, and since by far the largest part of the population changes sexual partner relatively infrequently, this assumption on prevalence will probably have only a small effect on the cost-effectiveness ratio.

In the low scenario, carrier prevalence in the general population of the Netherlands is estimated at 0.26 percent; in the intermediate scenario it is 0.42 percent; and in the high scenario it is 0.56 percent. The estimated incidence of new hepatitis B infections then works out at 18 per 100,000, 27 per 100,000 and 34 per 100,000 people respectively in the starting position, that is to say, before any form of preventive vaccination policy has been launched except the screening of pregnant women and the vaccination of the infant children of female HBV carriers. Because of the vaccination programme targeted towards high-risk groups, the incidence of new hepatitis B infections is lower than the 18 to 34 per 100,000 people just described. However, carrier prevalence in the base line scenario is thereby clearly higher than was assumed in earlier calculations. A recent publication reported an estimate of carrier prevalence in the Dutch population as being between 0.36 percent and 0.55 percent.[108] The present estimate incorporates all high-risk groups.

The incidence of new HBV infections calculated by the model is considerably higher than the actual incidence of acute hepatitis B found in notification data (see Chapter 5, Section 5.1), which is about 1.4 per 100,000 people. Possible explanations for this discrepancy include the following factors: the fraction of clinical infections in children is only 10 percent, rising to up to 33 percent in elderly people; people with a mild clinical infection and aspecific symptoms may not seek medical help; and finally, not all diagnosed infections are reported. Together, this accounts for considerable under-reporting of the disease.[106]

The results of the analysis with regard to incidence and prevalence are given below, starting from the intermediate scenario which employs a prevalence of 0.42 percent. The cost-effectiveness ratio is presented for all three prevalence scenarios.

The model assumes that the immigrant population mixes fully with the indigenous population, an assumption which the Health Council judged unlikely in earlier Health Council advisory reports.[1] Given the higher prevalence of carrier status amongst immigrant groups, this could yield an overestimation in the number of infections.

The model is subject to some uncertainty with regard to data on horizontal transmission, as quantitative data on the subject is scarce. Quantitative analysis has access to only limited data on infection mechanisms and contact patterns in horizontal transmission. The present model incorporates horizontal transmission for children from 0 to 14 years of age. The prevalence of carrier status in the Netherlands, as we have said, is principally dependent on the prevalence of carrier status amongst immigrants. The number of new HBV infections appearing amongst 0 to 14-year-olds is corrected for (estimated) under-reporting resulting from subclinical infection courses. This yields an estimate that 11 percent of all new HBV infections take place in this age group.[106]

The degree of contagiousness has been incorporated into the model as the likelihood of transmission between two people when one of them has an acute or a chronic infection. Little data is available on the relationship between hepatitis B viral load and contagiousness, so it has not been incorporated into the model.

9.2 Results of the cost-effectiveness analysis

The influence of different vaccination strategies on the incidence of hepatitis B infections

Figure 2 shows the results of modelling different vaccination strategies. The effects of these strategies have been displayed with respect to a 50-year time horizon. From a given starting point (the screening of pregnant women and the vaccination of the infant children of female carriers), two high-risk group scenarios have been modelled: the vaccination of infants with at least one parent from an intermediate or high-endemic country, and the vaccination of people in adult high-risk groups (from 2003).

The central question now is whether additional benefits can be derived by introducing the general vaccination of infant or prepubertal children alongside the existing high-risk group based vaccination policy. In the model, both general vaccination strategies are launched five years after the implementation of the last changes in the high-risk group based policy. If the general vaccination of prepubertal children is introduced, the vaccination of infant children with at least one parent from an intermediate or high-endemic country has to be continued. If the

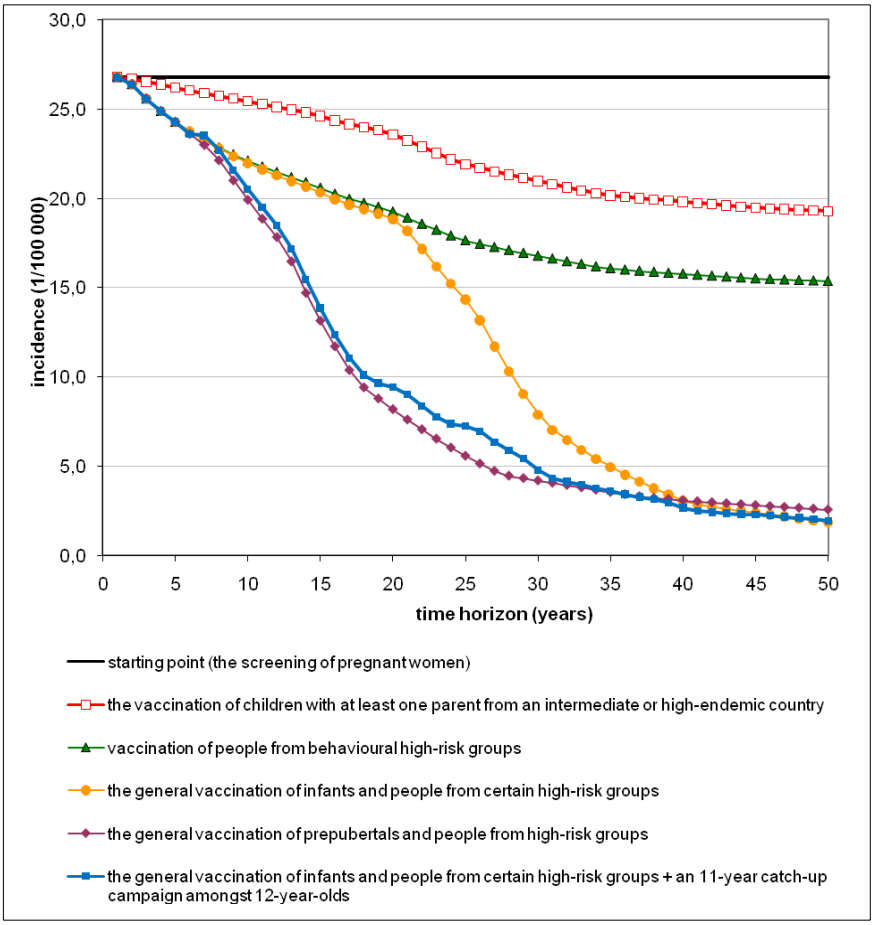

Figure 2 The effect of different vaccination strategies on the incidence of hepatitis B infections, shown over a period of 50 years. (Source: RIVM, 2009.)

general vaccination of infant children is introduced, the vaccination of this high-risk group is subsumed into the general vaccination programme. In both general vaccination strategies, the screening of pregnant women and the vaccination of the newborn children of HbsAg positive mothers must be continued. The vaccination of adults in high-risk groups must also be continued until, after a period of 20 to 40 years, this group has also been conferred protection by general vaccination. The calculations therefore include the vaccination of adults in high-risk groups for a period of 30 years. Finally, the model which introduces the general vaccination of infants includes an 11-year catch-up vaccination campaign amongst 12-year-olds.

The vaccination of people in high-risk groups eventually enables a 44 percent reduction in incidence levels, resulting in an incidence of about 15 cases per 100,000 people after 50 years. General vaccination strategies ultimately enable much greater reductions (over 90 percent), with incidence levels estimated at being between 2 and 3 per 100,000 people after 50 years. An important difference exists between the two general vaccination strategies: the general vaccination of infant children prevents all cases between the ages of 0 and 12 years that would otherwise arise in the current high-risk group based approach and with the vaccination of prepubertals. In Figure 2, this can be seen as the difference in incidence between 5 and 20 years (because of the assumption that people are sexually active from their 15th year onwards) between the vaccination of infant children with at least one parent from an intermediate or high-endemic country and the general vaccination of all infants.

Figure 2 shows that the incidence falls more quickly following the addition of general vaccination of prepubertal children than following the addition of the general vaccination of infant children. This is because most infections in the Netherlands are passed on via sexual contact. The general vaccination of prepubertals also yields a rapid fall in incidence, because this vaccination occurs close to the age at which people become sexually active. The general vaccination of infants causes this fall in incidence at a later date, unless a catch-up campaign to vaccinate 12-year-olds is carried out for 11 years. In that case, the fall in incidence is comparable to that achieved by the general vaccination of prepubertals, and ultimately this strategy yields the greatest reduction of new hepatitis B infections. The reach of the catch-up campaign has been assumed to be slightly lower (85 percent) than that for the general vaccination of prepubertals (90 percent), and this is why the incidence levels are a little lower for the general vaccination of prepubertals.

The influence of different vaccination strategies on the prevalence of carrier status

The effects of all vaccination strategies on the prevalence of carrier status are relatively small (see Figure 3 below). Most of the carriers found in the Netherlands come from intermediate and high-endemic countries, and these people can only be protected by vaccination in these countries. After 50 years, carrier status prevalence is most effectively reduced by means of the general vaccination of infant children and an 11-year catch-up vaccination programme amongst 12-year-olds.

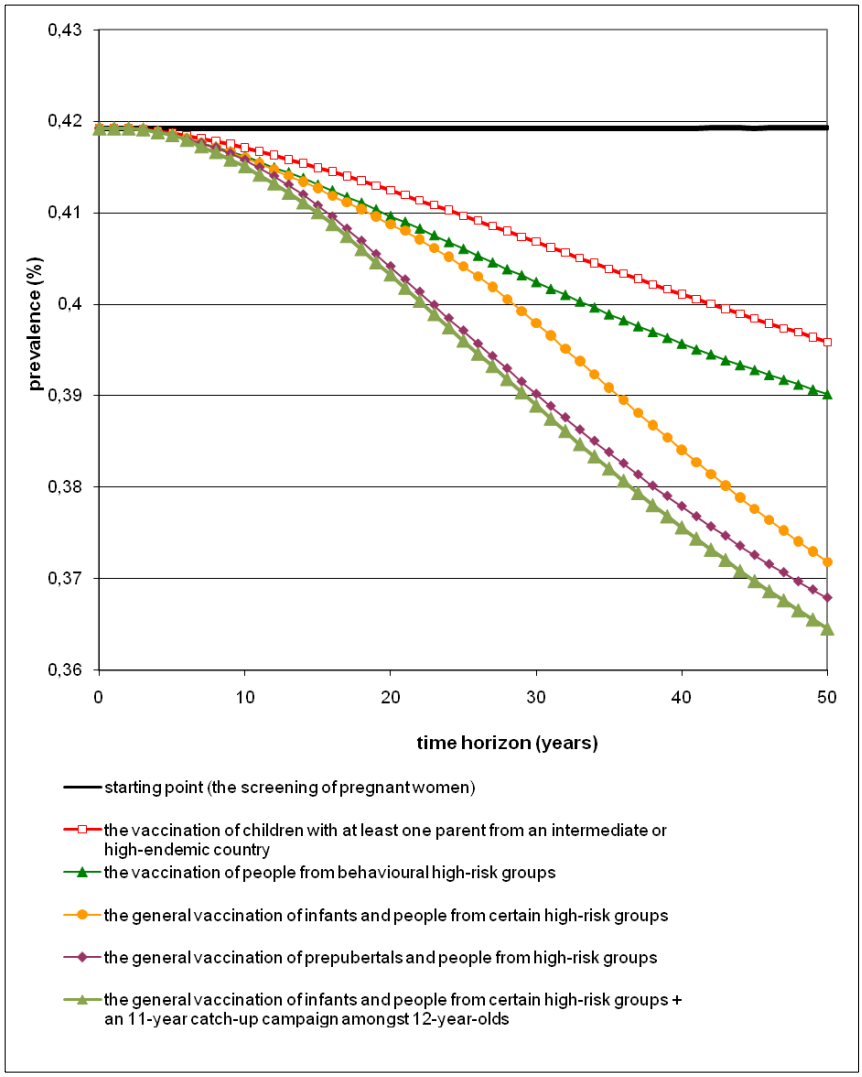

Figure 3 The effect of different vaccination strategies on the prevalence of carrier status (Source: RIVM, 2009.)

After 50 years, the progressive vaccination of people from all currently vaccinated high-risk groups yields a fall in carrier prevalence of about 7 percent, to a prevalence of 0.39 percent. The general vaccination strategies enable a reduction of about 12 percent, to a prevalence of about 0.37 percent.

The influence of the vaccination strategies on hepatitis B mortalities

Like the effects of the vaccination strategies on prevalence, their effects on the number of hepatitis-related deaths are relatively small, because most of the carriers are adult immigrants. Table 11 gives an overview of the model's predicted mortality rates for each vaccination strategy after 50 years and the total number of deaths prevented by each strategy. The expected number of prevented deaths is the difference between the number of mortalities expected under the starting situation and the predicted number of mortalities for each strategy. In some combined strategies, these prevented mortalities can be added together; for instance, the results of strategy C can be added to the results of strategies A and B. In general vaccination, certain high-risk group policies have to be maintained. The table index describes which strategies are being combined. Section 9.1 described how the model employs three scenarios for the prevalence of carrier status amongst immigrants; the table shows only the data yielded by the intermediate prevalence scenario.

The data in Table 11 show that general vaccination strategies enable the prevention of the greatest number of mortalities.

Table 11 The number of predicted mortalities and the number of prevented mortalities over 50 years per vaccination scenario and the absolute number of prevented mortalities. (Source: RIVM, 2008.)

vaccination strategy	total number of predicted mortalities	predicted number of prevented mortalities (absolute)
A	8,722	starting point
B	6,232	2,490
C	5,496	3,226
D	4,043	4,679
E	3,811	4,911
F	3,393	5,329

A: Starting point; screening pregnant women and vaccinating the infant children of carriers.
B: The vaccination of the infant children with at least one parent from an intermediate or high-endemic country, in addition to strategy A.
C: The vaccination of people in behavioural high-risk groups, in addition to strategies A and B.
D: The general vaccination of infants, in addition to strategies A and C.
E: The general vaccination of prepubertals, in addition to strategies A, B and C.
F: The general vaccination of infants, in addition to strategies A and C + an 11-year catch-up vaccination campaign amongst 12-year-olds.

The difference in the prevented number of mortalities between the two general vaccination strategies (infant or prepubertal children) can be explained by the way the model works. Since it initiates all the general vaccination strategies (vaccination of infant children at infant age and of prepubertal children at 12 years of age) in year 5, after 50 years more mortalities will be prevented by the vaccination of prepubertals because the reduction of incidence is effected more quickly. However, the committee expects that if the model were to be run for a longer period, at least as many mortalities, and probably more, would be prevented by the general vaccination of infants. The greatest number of fatalities are expected to be prevented when a catch-up campaign is implemented alongside the general infant vaccination strategy. This catch-up strategy is discussed in more detail in the section on the costs-effectiveness ratio of a catch-up vaccination campaign for 12-year-olds.

The cost-effectiveness ratios of the vaccination strategies

As was described in the introduction to this chapter, the cost-effectiveness ratio of a programme is expressed in terms of the cost per QALY thereby obtained. In the Netherlands a preventive programme is generally deemed to be cost-effective if its costs are below 20,000 euro per QALY gained. The cost-effectiveness ratio of the high-risk group approach may be said to be very favourable: for the vaccination of the infant children of parents from intermediate or high-endemic countries it lies, depending on the prevalence scenario (low, intermediate or high, see Section 9.1), at 700, 300 or 100 euros per QALY gained, respectively. For the vaccination of people from behavioural high-risk groups it amounts to about 3 500, 2 300 or 1 800 euro per QALY gained, respectively.

The general vaccination strategies also have a favourable cost-effectiveness ratio which does not exceed 5,000 euro per QALY gained – in other words, well below the threshold value of 20,000 euro per QALY gained generally employed in the Netherlands. For the general vaccination of infant children, the cost-effectiveness ratio – again, depending on the prevalence scenario (low, intermediate or high), is around 4,800, 3,100 or 2,300 euro per QALY gained, respectively. For the general vaccination of prepubertals, it amounts to about 4,200, 2,700 or 2,000 euro per QALY gained, respectively.* Here, too, the difference in cost-effectiveness ratio between both general vaccination strategies is partly the result of time horizon, as described in the previous section. There is also some uncertainty with regard to the costs of introducing vaccination for prepubertal chil-

* A. de Wit, M. Kretzschmar (RIVM), written communication, 2007.

dren, since it entails the creation of a new infrastructure for its administration. The influence of these costs on the cost-effectiveness ratio of a general vaccination programme for prepubertal children is given in Section 9.3.

The cost-effectiveness ratio of a catch-up vaccination programme for 12-year-olds

The beneficial effects of a general hepatitis B vaccination programme for infants alone emerge only over a longer period of time, as can be seen in Figure 2. Because these effects are delayed, a large additional group of young children can usefully be protected by means of a catch-up vaccination campaign at the age of 12 years. This means that the beneficial effect of vaccination on disease incidence will be visible 12 years earlier than it would have been with infant vaccination alone. Ultimately, this also gives earlier protection to adults in high-risk groups. At the committee's request the RIVM researchers modelled an 11-year catch-up campaign amongst 12-year-olds, which would yield an annual cohort of 12-year-olds protected against hepatitis B.

When vaccinating at this age, the possibility of delivering a combined vaccine against HPV and HBV should be considered. Both vaccinations could be administered at the same contact moments to girls, but separate vaccination moments would also be an option. Both strategies – that is to say, vaccination against HPV and HBV at different contact moments and vaccination against both at the same contact moments – include a contact moment with a paediatrician. For vaccination at the same contact moments, both vaccinations are given three times to allow the programmes to take the same course as far as possible and to thereby share the implementation costs. If separate vaccination were to be chosen, then it is assumed that two vaccinations against hepatitis B would be sufficient. Both scenarios assume a reach of 85 percent, as estimated in the advisory report *Vaccination against cervical cancer.*[103]

After 50 years the catch-up vaccination campaign will have prevented an estimated 650 extra mortalities. Depending on the prevalence scenario (low, intermediate or high), the cost-effectiveness of a catch-up campaign carried out simultaneously with vaccination against HPV for girls is 10,400, 6,900 or 5,200 euro per QALY gained, respectively. When the catch-up campaign is carried out separately from vaccination against HPV, the cost-effectiveness ratio is 12,500, 8,300 or 6,300 euro per QALY gained, respectively.*

* A. de Wit (RIVM), written written communication, 2008.

9.3 Sensitivity analysis

Sensitivity analysis assesses the effect of variation in the assumed values of certain model parameters.

The general vaccination of infants requires three doses, while DPT-polio-Hib is currently given in four doses (such as DPT-polio-Hib-HepB in the infant children of parents from intermediate or high-endemic countries). The basic analysis was calculated using three doses.

Vaccine administration in three doses is more complicated: three doses of hexavalent vaccine must be given and a single dose of pentavalent vaccine. In the sensitivity analysis, the researchers used four doses. When using four doses, the cost-effectiveness ratio changes from about 4,800 to 6,600 euros per QALY gained (low prevalence), from about 3,100 to 4,300 euros per QALY gained (intermediate prevalence) from about 2,300 to 3,200 euros per QALY gained (high prevalence).*

Another important aspect is formed by the costs of setting up the infrastructure for the vaccination of prepubertal children. In the basic modelling of general prepubertal vaccination, these costs have been estimated at 2 million euros per year (85 percent of the adolescents are administered two vaccinations at school), but in the sensitivity analyses these costs were assumed to be higher, namely 10 million euros per year. This last analysis envisages a separate infrastructure for the vaccination of prepubertal children, with a contact moment with a paediatrician and two follow-up vaccinations in school time. This infrastructure could be shared with the vaccination against HPV, and for this reason a scenario with costs of 5 million euros per year (attributable to the hepatitis B vaccination) was also worked up. The results of these assumptions on the cost-effectiveness ratio are shown in Table 12 on the next page.

* A. de Wit, M. Kretzschmar (RIVM), written communication, 2007.

Table 12 Sensitivity analysis: the influence of implementation costs on the cost-effectiveness ratio of general vaccination of prepubertals compared with high-risk group vaccination. (Source: RIVM, 2007.)

implementation costs of general vaccination for prepubertals	cost per QALY (euro) per prevalence scenario		
	low	intermediate	high
two million euro	2,000	2,700	4,200
five million euro	3,100	4,200	6,400
ten million euro	5,000	6,600	10,000

9.4 Conclusion

A programme which includes general vaccination can prevent considerably more HBV infections and mortalities than can a high-risk group based approach; such a general programme is also cost-effective

The committee concludes that, in the long term, a programme which includes general vaccination can achieve significant extra health benefits, compared to a high-risk group based programme alone. Like the high-risk group based approach, such a programme is cost-effective, with a cost-effectiveness ratio which lies well below the threshold of 20,000 euros per QALY gained which is generally used in the Netherlands. However, the cost-effectiveness ratio of general prepubertal vaccination can vary because of its dependence on the size of the implementation costs, an issue which does not arise in general infant vaccination. The committee is of the opinion that if it were decided to introduce general infant vaccination, this should be combined with a catch-up vaccination campaign amongst 12-year-olds so as to expedite the considerable health benefits that arise. At the same time, this approach also yields the greatest health benefits. The catch-up vaccination is also cost-effective.

Chapter 10

The urgency of vaccination

The final inclusion criterion (criterion seven) concerns an assessment of the priority of hepatitis B vaccination compared to other vaccinations that might prevent significant public health problems.

10.1 Other candidates for vaccination, and weighing up different aspects

The advisory report *The future of the National Immunisation Programme: towards a programme for all age groups* listed four vaccinations which needed additional analysis and advice in the short to medium term: vaccination against cervical cancer, general vaccination against hepatitis B, against rotavirus infection, and against shingles/chickenpox.

Since then the Health Council has published an advisory report on vaccination against cervical cancer, which it estimates could prevent 300 illnesses and 100 deaths per year. The council recommended that vaccination for girls be included in the NIP. On the basis of illness reporting data, the minimum number of additional cases of disease that could be prevented by general vaccination against hepatitis B is of the same order of magnitude, and the number of mortalities prevented is lower, but the actual number of cases of disease and death caused by hepatitis B are probably considerably higher.

Rotavirus infection-induced diarrhoea and chickenpox do frequently occur in the Netherlands but these diseases are less serious than hepatitis B, and the cost of vaccinating against rotavirus and chickenpox is relatively high. Shingles is a

fairly common and quite serious illness amongst the elderly in particular, for which vaccination has recently become possible. However, the disease burden prevented by vaccination is, as yet, unclear.

10.2 Conclusion

The committee concludes that general vaccination against hepatitis B addresses an important public health problem, and that compared to other candidate vaccines, deserves to be given priority.

Chapter **11**

Weighing up possible strategies

In the previous chapters, the adoption of general strategies for vaccination against hepatitis B in the NIP was tested against the seven criteria for inclusion of vaccinations in public programmes. Three scenarios were considered: 1) maintaining the current policy of vaccinating only people from high-risk groups, 2) supplementing this policy with general infant vaccination, and 3) supplementing this policy with general prepubertal vaccination. Each of these scenarios has its own advantages and disadvantages, as their assessment by reference to the criteria has illustrated. In this chapter, the committee presents a summary of the advantages, disadvantages and uncertainties attached to each scenario, and closes by expressing its own preference.

11.1 An overview of the considerations per scenario

11.1.1 The vaccination of high-risk group members only

Arguments for continuing this policy

- The incidence of new HBV infections in the Netherlands is low, and three-quarters of all new infections occur in familiar high-risk groups.
- When *all* those who run the risk of being infected with the hepatitis B virus can be reached by means of a selective vaccination programme, then this approach places no extra burden on the rest of the population. However, all

those whose circumstances or behaviour approach risk group status must be adequately protected for this approach to succeed.
- Those people who run no risk of infection do not need to be vaccinated.
- The current programme is cost-effective.

Arguments against continuing this policy

- People in behavioural high-risk groups can run risks before they realise that they actually belong in a high-risk group. The protection conferred by vaccination may then arrive too late or not at all.
- There are as yet no clear indications that the incidence of new HBV infections is falling.
- The identification and vaccination of people from certain high-risk groups is very labour-intensive. Despite considerable efforts, it appears that the reach of existing programmes in some important high-risk groups, such as homosexual men, is inadequate.
- Risk group based programmes do not reach everyone running the risk of infection: a quarter of the reported new cases of acute hepatitis B infections in the Netherlands are not attributed to a known risk factor.

Uncertainties

- The limits of the existing high-risk group policy appear to have been reached. It is unclear whether this high-risk group policy can be intensified any further.
- It is uncertain whether the degree of intensiveness of this policy can be sustained for many years to come.
- It is uncertain whether this approach can reduce the incidence of new HBV infections any further.

11.1.2 Programme expansion to include general infant vaccination

Arguments for this expansion

- A programme which includes general infant vaccination alongside the vaccination (for a limited period of time) of people from certain high-risk groups can bring about considerably greater health benefits compared with the vaccination of high-risk group members alone. Over a period of 50 years, it would appear to yield a 90 percent reduction in the number of new HBV infections and a substantial drop in mortality.

- The vaccination is easy to introduce: The injection burden stays the same if a combined vaccine with a hepatitis B component can replace the existing DPT-polio-Hib vaccine.
- The reach of infant vaccination programmes within the NIP is high: above 95 percent. If this reach is retained after the inclusion of vaccination against hepatitis B, this will yield the greatest possible health benefits.
- Once infected, the likelihood that a young person develops carrier status is extremely high, while at the same time the course of the infection is often asymptomatic. This intervention would prevent such infections and their consequences.
- This approach means that all those who become infected but who are not members of the usual high-risk groups are also protected.
- The hepatitis B vaccine has been found to be safe and effective, including when used for infant vaccinations.
- The general vaccination of infant children is acceptable. This applies both at the level of individual vaccination and to the entire NIP.
- Modelling research has found the general vaccination of infants to be cost-effective.
- It allows the existing programme of vaccination for the infant children of parents from intermediate and high-endemic countries to be dropped, since these children are immediately covered by the general programme. The reach in this group provided by the general programme may actually be greater.
- After a period of time, the vaccination of adults from high-risk groups can also be dropped.

Arguments against this expansion

- In general, children below the age of puberty run a relatively low risk of being infected with the hepatitis B virus in the Netherlands. This means that it will generally be longer (about 20 years) before a clear drop in incidence is seen, unless a catch-up vaccination campaign for older children is implemented.

Uncertainties

- It is not yet entirely clear how long hepatitis B vaccination confers protection against viral infection. However, there are no clear indications that this protection has fallen significantly since the vaccine was introduced about 26 years ago.
- It is uncertain whether the >95 percent reach that NIP vaccinations currently have amongst infants will be sustained if hepatitis B vaccination is added.

11.1.3 Programme expansion to include general prepubertal vaccination

Arguments for this expansion

- Greater health benefits can be achieved when all prepubertal children are vaccinated alongside people from high-risk groups, compared to the vaccination of high-risk group members alone.
- Those risking viral infection but who currently fall outside the usual high-risk groups would be protected against such infection from the age of 12 years.
- Vaccination against hepatitis B has been found to be effective and safe, including when used for prepubertal children.
- Modelling research has found the general vaccination of prepubertal children to be cost-effective.
- After a lengthy period of time, it will also be possible to drop the vaccination of adults in high-risk groups.
- The vaccination of prepubertal children takes place shortly before the age at which infection risks, and sexual contacts in particular, appear.
- No catch-up vaccination campaign is required; the intended preventive effects are achieved immediately.
- There is relative certainty of protection in the period during which most infections take place.
- The general vaccination of prepubertal children is acceptable. This applies both at the level of individual vaccination and to the entire NIP.
- The general vaccination of prepubertal rather than infant children avoids potential argument about the acceptability of vaccinating infants against a disease that is (also) sexually transmitted.

Arguments against this expansion

- New contact moments have to be set up in order to administer the vaccination of 12-year-olds.
- Extra injections have to be given, compared to the existing NIP.
- Not all infections occurring before the age of 12 are prevented. In young children, hepatitis B infections are often asymptomatic and the risk of developing carrier status is very high.
- The directed vaccination of the infant children of parents from intermediate and high-endemic countries has to be continued.

Uncertainties

- The level of vaccination coverage amongst prepubertal children is unknown, as no vaccinations have yet been given in the Netherlands to this age group. The Health Council earlier estimated the level of coverage in the vaccination of girls against cervical cancer at 85 percent.
- The costs of setting up the new contact moments are still uncertain, and these costs have a significant influence on the cost-effectiveness ratio of general prepubertal vaccination.
- It is not yet entirely clear how long the hepatitis B vaccine confers protection against viral infection. However, there are no clear indications that this protection has fallen significantly since the vaccine was introduced about 26 years ago.

11.2 An assessment of the strategies

The point-by-point summary above makes it clear that effectiveness and appropriateness play an important role in the assessment of the three vaccination scenarios under consideration. The underlying question is always: to what extent can those groups who run the greatest risk of hepatitis B infection be reached, and which scenario yields the greatest health benefit at an acceptable cost?

In its advisory report of 2007 the Health Council judged that the high-risk group approach met inclusion criterion 2 (the effectiveness of vaccination). Upon closer examination it appears that the programme's reach, especially in the behavioural high-risk groups, is inadequate. There is significant room for improvement, and general vaccination offers the possibility of achieving this improvement.

With regard to the assessment of efficiency (inclusion criterion 6, Chapter 9) it appears that health benefits could be substantially increased by electing to implement a general vaccination approach alongside the existing high-risk group based approach.

The safety of the vaccines used within the NIP is of great importance. After years of practical experience with hepatitis B vaccination, the available data on its adverse side effects shows that vaccination against hepatitis B is safe. The frequency of side effects is low, and the adverse effects that do appear are almost invariably mild and transient in nature. These side effects do not detract from the health benefits that vaccination confers, and in Chapter 7 the committee concluded that the safety profile of hepatitis B vaccination forms no impediment to the administration of vaccination to all infant or prepubertal children.

In Chapter 8 the committee discussed the acceptability of general vaccination. The committee concluded that the public interest was served by general vaccination. The analyses presented in Chapter 9, which compared the effectiveness of the high-risk group based approach with that of general vaccination, showed that general vaccination yielded substantial extra health benefits for the population as a whole. It was also expected that those groups most urgently in need of protection from infection would also be reached more effectively by general vaccination.

There are therefore good reasons to make the move to general vaccination. Both options, namely the vaccination of infant or of prepubertal children, are reasonable choices, but the committee favours infant vaccination.

An important consideration with regard to the acceptability of such a programme is the limitation of the burden for participants in the NIP. The general vaccination of infant children allows the injection burden to remain the same, when use is made of a combined vaccine. Because of the absence of an additional injection burden, and given the public health interest, the committee considers the general vaccination of infant children, using a combined vaccine, to be acceptable. The vaccination of prepubertal children forms a possible alternative to the general vaccination of infants; however, this necessitates extra injections and new vaccination sessions. The burden imposed by these are nevertheless limited and, in the committee's opinion, also acceptable.

If it is decided to introduce general infant vaccination against hepatitis B, the committee recommends the implementation of an 11-year catch-up vaccination programme amongst 12-year-olds. In this way, population immunity can be brought to a relatively high level in a short period of time.

Chapter **12**

Recommendations for implementation

Should it be decided to introduce general infant vaccination against hepatitis B together with a catch-up vaccination programme for 12-year-olds, or the general vaccination of prepubertal children, then this decision necessitates a number of measures which will have an influence on the NIP or which are of vital importance to its satisfactory implementation. For instance, the current NIP includes programmes which could either be halted or must be continued. The choice of age group to which a catch-up vaccination is given also has organisational consequences. Information must also be given to immunisation organisations and to parents, if public willingness to participate, and the degree of vaccination coverage that is directly linked to this willingness, are to be safeguarded. Finally, the monitoring of safety, degree of coverage, and effectiveness forms a precondition for the introduction of any vaccination. In this chapter the committee gives a list of these measures.

12.1 The vaccination of the infant children of HbsAg positive mothers should be evaluated

Since the passive and active immunisation of the children of HbsAg-positive mothers has to be administered directly after birth, this cannot be subsumed by a general vaccination policy which gives infants their first vaccination at the age of two months. The screening of pregnant women and the passive and active immu-

nisation of their children immediately after birth must therefore remain in place, no matter which other immunisation programme is adopted.

About 90 percent of all pregnant women are screened for carrier status. The committee attaches great value to this programme, and has recommended looking into how its reach could be further improved. To this end a committee has been set up at the CvB, which advises directly on the national implementation of the programme.

These children are presently checked by means of serological response studies after vaccination. It is precisely because these children run such a high risk of infection that it is vital that they are accorded adequate protection. It is of abiding importance that all children of HBsAg-positive mothers are tested to establish the effect of vaccination after the series of injections has been completed.

12.2 Carry out test studies of acceptance

An extremely beneficial attribute of the NIP is its current high level of vaccination coverage. It is vital that this is not compromised, and the committee therefore recommends that test studies be carried out into ways in which the acceptance of general vaccination against hepatitis B can be maximised and any possible negative effects on other vaccinations be minimised.

12.3 The vaccination of people in high-risk groups must be continued

If a general infant vaccination programme were to be adopted, the current vaccination programme for the high-risk group of children with at least one parent from a country in which hepatitis B is prevalent could be halted. These vaccinations would then be given within the NIP and subsumed within the general vaccination of infant children. However, this would not hold if the general vaccination of prepubertal children were adopted; in that case this programme would have to be continued, just as it must naturally be continued if it is decided not to switch to general vaccination at all but to continue the current high-risk group based programme.

Vaccination programmes for people in adult, behavioural high-risk groups, and for people who run a raised risk of infection because of the nature of their professional work, must also remain in place. In general vaccination strategies, the vaccination of these groups can be terminated after a period of 20 to 40 years, when their members have been reached by general vaccination as infant or prepubertal children and when it has been established beyond doubt that this vaccination confers adequately long-lasting protection. Until then, these groups

continue to run a raised risk of infection of being infected with HBV. The issues of immigration and professional risk will continue to make the separate vaccination of unprotected people necessary in certain cases.

12.4 Seek integration with existing vaccination regimes

To keep the organisational consequences as minimal as possible it was decided, in the high-risk based approach towards the infant children of parents from intermediate or high-endemic countries, to administer four doses of a combined vaccine with a hepatitis B component, even though only three separate doses would have been needed to protect against hepatitis B. The committee recommends that the same approach is adopted if it is decided to switch to general infant vaccination.

If it is decided to introduce the general vaccination of prepubertal children, then the committee recommends that for girls this employs the same contact moments as those where vaccination against cervical cancer is administered. In order to bring about the desired level of protection as quickly as possible, the committee also recommends that the same schedule is employed for both vaccinations (the second dose after one month and the third after six months).

12.5 Combine catch-up vaccination with vaccination against cervical cancer

In the previous chapter the committee recommended that a catch-up vaccination programme should be set up if it is decided to introduce the general vaccination of infant children. A two-dose schedule confers adequate protection only after the last vaccination, that is to say, after 6 months; the committee therefore recommends that a three-dose schedule be maintained.

The Dutch child health care system provides a consultation (with no injections) for certain children at the age of thirteen. The committee deems this moment to be too late because there are indications that children start to become sexually active at the age of twelve. The committee recommends that the catch-up vaccination be administered at the age of twelve, for girls simultaneously with the HPV vaccination.

12.6 Provide effective public information and education

The introduction of general vaccination against hepatitis B should be coupled with the provision of accurate and effective information on the subject, taking

into account the needs of population groups with different cultural, ethnic and religious backgrounds – and in the case of general infant vaccination, for both parents and immunising organisations. If a catch-up vaccination campaign for 12-year-olds is set up to accompany general infant vaccination, or if the general vaccination of prepubertal children is introduced, then these children must also be given clear explanatory information on the subject. The general vaccination of prepubertal children and a catch-up vaccination programme for 12-year-olds are both aimed at vaccinating against an infection which in the Netherlands is often transmitted by sexual contact from this age upwards.

If the seriousness of an HBV infection, the high risk run by young children of developing carrier status, and the possibilities of prevention and treatment are not well known and understood, this can damage the prospects for the acceptance of vaccination and therefore lower the level of vaccination coverage. The provision of information is discussed in the Health Council's advisory report *The future of the National Immunisation Programme: towards a programme for all age groups*.

12.7 Monitor effectiveness and safety

It is vital that a specific monitoring programme is set up in order to safeguard the effectiveness of hepatitis B vaccination within the NIP. Besides actively monitoring the degree of vaccination coverage amongst those designated for vaccination and the registration of side effects, as is usual in public vaccinations, the committee recommends that links are made between vaccination registers and illness registers so that any unusual side effects that do arise are quickly detected.

The committee has indicated that the monitoring of immunity against hepatitis B is very important, and forms a precondition for the introduction of general infant vaccination. This should preferably be carried out by an independent scientific body such as the RIVM. This will yield reliable national data by reference to which an informed decision can be made on whether the catch-up vaccination campaign should be converted into a one-off booster vaccination in order to guarantee long-term protection against hepatitis B. This study will have to examine not just sero-protective antibody titres but in particular the presence of effective immune memory, such as the capacity to initiate a rapid immune response (which is an indicator of immune memory) after the administration of a booster vaccination of hepatitis B vaccine. This will yield data on immune memory and on the capacity to initiate an adequate immune response after viral infection.

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Annexes

Annex **A**

Background to this advisory report

At the request of the Minister of Health, Welfare and Sport (VWS), the Health Council published a general advisory on 7 March 2007 entitled *The future of the National Immunisation Programme: towards a programme for all age groups*. This report described an assessment framework and seven criteria by which the proposed inclusion of a vaccine within a public vaccination programme could be evaluated. The standpoints described in the report were subsequently adopted by the Minister.

The same report included an assessment of the current high-risk group approach towards vaccinating children against hepatitis B, which the Health Council judged to be an sustainable approach. The Health Council also evaluated the proposed inclusion of general vaccination against hepatitis B in the National Immunisation Programme. Hepatitis B was seen as an illness with a considerable individual burden, which carrier status could impose on a much wider group of people. At that time, definitive advice on general vaccination against hepatitis B could not be given because the effectiveness and efficiency of the vaccine was not yet known.

At the same time it was not known which strategy was most appropriate to the introduction of general vaccination: the vaccination of infant or of prepubertal children. The Health Council concluded that supplementary analysis was required in the short term. To facilitate this analysis, the RIVM carried out a cost-

effectiveness study in order to assess the effectiveness and efficiency of general vaccination. These calculations made use of models that were modified with regard to earlier shortcomings to better apply to the situation in the Netherlands, including the use of more realistic, lower vaccine costs. The cost-effectiveness ratio was subsequently found to be well below the threshold generally employed in the Netherlands. These models have now also made it possible to make comparisons between the high-risk group approach and general vaccination strategies.

Annex **B**

The committee and consulted experts

National Immunisation Programme committee

- Professor E.J. Ruitenberg, *chairman*
  Emeritus Professor of Immunology, Utrecht University; Professor of International Public Health, *VU* University, Amsterdam
- Professor J.J. Roord, *vice chairman*
  Professor of Paediatrics, *VU* University, Amsterdam
- Dr. M.A.E. Conyn-van Spaendonck, *advisor*
  Physician, epidemiologist and National Immunisation Programme manager, Centre for Infectious Disease Control (CIb), Netherlands National Institute for Public Health and the Environment (RIVM), Bilthoven
- Dr. P.J. van Dalen, *advisor*
  Ministry of Health, Welfare and Sport, Den Haag
- Professor W. van Eden
  Physician, microbiologist and Professor of Veterinary Immunology, Utrecht University
- Professor R. de Groot
  Professor of Paediatrics, Radboud University Nijmegen
- Dr. H.E. de Melker, *advisor*
  Epidemiologist, Netherlands National Institute for Public Health and the Environment (RIVM), Bilthoven
- Dr. T.G.W.M. Paulussen
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The committee consulted the following experts and institutes:

- Professor A. de Boer, Professor of Pharmacotherapy, Utrecht University
- F. Destefano, MD MPH, Senior research epidemiologist, RTI International, Atlanta, USA
- M. Girard, MD Msc, Versailles
- T. Gudnason, MD, Centre for Health Security and Infectious Disease Control, Seltjarnarnes, Iceland
- S. Hahné, Centre for Infectious Disease Control (CIb), Netherlands National Institute for Public Health and the Environment (RIVM), Bilthoven
- Professor M.A. Hernán, Harvard School of Public Health, Boston, USA
- Professor H.L.A. Janssen, Professor of Hepatology, Erasmus University Rotterdam
- Professor T. Jefferson, Cochrane Vaccines Field, Rome, Italy

- Dr D. Kennedy, Department of Health, Londen, United Kingdom
- Dr M.E.E. Kretzschmar, health economist, Centre for Infectious Disease Control (CIb), Netherlands National Institute for Public Health and the Environment (RIVM), Bilthoven
- Dr T. Leino, MD, National public health institute (KTL), Helsinki, Finland
- Dr Y. Mikaeloff, MD, Service de Neurologie Pediatrique, Angers, France
- Dr H. Nøkleby, MD, National Institute of Public Health, Oslo, Norway
- Professor C.H. Polman, VUmc Medical Centre, Amsterdam
- Dr S. Poulsen, MD MPH, National Board of Health, Copenhagen, Denmark
- Dr P. Ruutu, National public health institute (KTL), Helsinki, Finland
- Dr A. Tegnell, MD, Communicable disease prevention and control unit, National board of health and welfare, Stockholm, Sweden
- Dr L. Thornton, public health expert, Health Protection Surveillance Centre (HPSC), Dublin, Ireland
- Dr G.A. de Wit, health economist, Centre for Health Care Research (CZO), Netherlands National Institute for Public Health and the Environment (RIVM), Bilthoven
- the Netherlands Vaccine Institute (NVI), Bilthoven
- Agence française de sécurité sanitaire des produits de santé (AFSSAPS), France
- Dr R.T. Chen, MD MA, Centers for Disease Control and prevention (CDC), Atlanta, USA
- Commission nationale de pharmacoviligance, France
- The Superior Health Council (SHC), Brussels, Belgium
- National Centre for Immunisation Research and Surveillance (NCIRS), Westmead, Australia
- World Health Organization (WHO), Geneva, Switzerland

The Health Council and interests

Members of Health Council Committees – which also include the members of the Advisory Council on Health Research (RGO) since 1 February 2008 – are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions

they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Hepatitis B vaccination and multiple sclerosis

Summary

A link between hepatitis B vaccination and multiple sclerosis?

In 2004 a research study was published in the UK which found a statistically significant link between hepatitis B vaccination and the later onset of multiple sclerosis (MS). Such a link would have serious implications for existing and future vaccination programmes against hepatitis B. Are there indeed scientific indications of a link between hepatitis B vaccination and MS? This advisory report presents the judgement of the National Immunisation Programme committee on this question.

Assessment

Design and implementation of the research

The committee has examined the evidential value of the research study carried out by Hernán and his colleagues, and has concluded that it would be unreasonable to contend that the findings could be explained by shortcomings in the design or implementation of this study. However, the study concerns observational research that as such cannot furnish proof of a causal link between hepatitis B vaccination and MS because it is impossible to remove every possibility of epidemiological bias.

Pooled research

In order to better compare the research work done by Hernán and his colleagues with the results of other research studies, the Health Council commissioned a systematic review of the epidemiological research that has been carried out into the link between hepatitis B vaccination and MS. The pooled research gives no indications for a link between hepatitis B vaccination and MS.

The committee concludes that compared to other researchers Hernán and his colleagues examined the question of a link between hepatitis B vaccination and the later onset of MS with particular care and attention.

The plausibility of a causal link

The committee then reflected on whether a plausible explanation can be given for the posited causal link between hepatitis B vaccination and the subsequent onset of multiple sclerosis. The scientific literature has suggested that identical amino acid sequences appear in an enzyme of the hepatitis B virus (Hepatitis B virus polymerase, or HB-pol) and in the myelin sheath of nerve fibres. It is conceivable that molecular mimicry could induce an autoimmune process in susceptible persons.

However, HB-pol forms no part of the recombinant vaccine; at most, it might appear in the form of a trace contamination. It is therefore extremely unlikely that the vaccine would provoke an autoimmune reaction. HB-pol does form part of the hepatitis B virus itself, however, and is found in relatively high concentrations in persons with an active HBV infection. In countries like the United Kingdom (and the Netherlands), it is precisely those people who run a higher risk of infection who are selected for vaccination. In these countries, therefore, it is vaccinated people who run the greatest risk of coming into contact with the virus and becoming infected. This might explain the statistical link between vaccination and MS found by Hernán. The link would then actually be between infection with the hepatitis B virus and MS. The apparent link with vaccination would arise because precisely those people running the greatest risk of catching the disease would be selected for vaccination against it: this problem is known as ‘confounding by indication’.

In the committee’s opinion, molecular mimicry does not form a logical causal explanation for a posited link between hepatitis B vaccination and MS. It does, however, form a possible alternative explanation for the findings of Hernán and his colleagues.

Conclusion

On the basis of the available data, the committee has concluded that a link between hepatitis B vaccination using recombinant hepatitis B vaccine and MS is improbable.

Chapter 1

Introduction

1.1 A link between hepatitis B vaccination and multiple sclerosis?

In 2004 Hernán and his colleagues published a paper which has since been the subject of much discussion. It reported on a research study which claimed to have found a statistically significant link between hepatitis B vaccination and the later onset of multiple sclerosis (MS) in the United Kingdom. Although from a statistical perspective we may expect such a link to occasionally arise by chance, rather than because of any causal link with vaccination, this study points up the need for closer examination.

As in the UK, in the Netherlands certain high-risk groups are vaccinated against hepatitis B, including the children of hepatitis B carriers and all infants with at least one parent from a country with an intermediate to high prevalence of hepatitis B. This vaccination prevents a great deal of illness. If a link existed, or could exist, between this vaccination and MS, then from a precautionary perspective it is important to establish what implications this could have for existing and future vaccination programmes.

For this reason, the present report answers the following question:

How probable is it, on the basis of Hernán's findings, other recent research, and scientific knowledge of the mechanisms for a possible causal link, that hepatitis B vaccination is associated with a raised risk of MS?

1.2 Committee and working methods

The National Immunisation Programme committee has closely examined this question by studying the scientific literature on the subject and by consulting experts at home and abroad (a list of which can be found in Appendix B).

The committee also commissioned Professor T. Jefferson and colleagues from the Cochrane Vaccine Field in Rome to update their 2003 systematic review of research into possible links between hepatitis B vaccination and demyelinising disease, including multiple sclerosis (Appendix D).

1.3 Summary of chapter contents

Chapter 2 starts with some background information on hepatitis B vaccination in the Netherlands, on MS, and on its incidence in the Netherlands, and the Health Council's earlier evaluation of a possible link. In Chapter 3 the new research results are evaluated and compared with other recent findings. It also discusses whether a mechanism might conceivably exist by which a hepatitis B vaccination could lead to MS.

Chapter 2

Background information on hepatitis B and MS

2.1 Vaccination against hepatitis B in the Netherlands

Infection with the hepatitis B virus (HBV) is one of the causes of hepatitis (inflammation of the liver). The clinical symptoms of HBV infection vary from a subclinical infection with no jaundice, through transient general complaints and jaundice, to – in fewer than 1 percent of cases – acute liver failure with haemorrhaging, neurological problems, coma and death. The overwhelming majority of previously healthy people experience a transient infection; however, the immune system of some people is unable to clear up the virus and these people become chronically infected 'virus carriers'. There are close correlations between infection at a young age, asymptomatic infection with no jaundice, and the acquisition of carrier status; if no preventive treatment is given, over 90 percent of newborns who are infected with the virus go on to develop carrier status. This rate falls quickly with infection at a later age, to about 10 percent at 15 years of age. The rate then continues to fall gradually to about 4 percent amongst 35-year-olds and to 2 percent amongst 55-year-olds.[1] Protracted chronic infection can give rise to liver cirrhosis and liver cancer. HBV carriers form an important factor in the continuing spread of hepatitis B.

Because of the seriousness of the disease, the Netherlands has pursued a programme of public vaccination against hepatitis B for a number of specific groups. Since 1989 all pregnant women have been screened for the presence of the hepatitis B virus; if they are found to be a carrier, their newborn child is vac-

cinated as soon as possible after birth to avoid the risk of its also becoming chronically infected.

On the Health Council's advice, in 2003 preventive vaccination against hepatitis B was introduced for all infant children with at least one parent from a country in which hepatitis B is prevalent.

Since 2002 the Netherlands has also intensified its vaccination programme for people in specific high-risk groups; this concerns principally people with a variety of homosexual or heterosexual contacts, and intravenous drug users.

Finally, health workers are often vaccinated, and members of the police force and municipal waste operatives are occasionally vaccinated, as a precautionary measure within the framework of their professional responsibilities.

2.2 The prevention of multiple sclerosis in the Netherlands

MS is a slowly progressive disease of the central nervous system characterised by apparently random attacks of neurological dysfunction. The symptoms are caused by an apparently equally random pattern of damage to the myelin sheath of the body's nerve fibres. The diagnosis of MS is a complex matter and is still in development.[2,3] It is widely held that MS arises in an interplay of genetic and environmental factors, but it is not yet known exactly what actually causes MS. Smoking, being female, and being younger than 40 are all risk factors. Although it was long assumed that the disease mechanism of MS had principally to do with auto-immunity, there are recent indications that it might be a neurodegenerative illness, in which case any immunological symptoms would be secondary.[4,5]

Although MS is not common, it is still the most prevalent chronic neurological disease in young adults, occurring in about one in a thousand people, and in the long term it can result in permanent disability. There is, however, no clear link between objective disease indicators, such as muscle weakness and the scale of myelin lesions detected on the one hand, and in the quality of life on the other; psychological factors, such as coping, mood, personal effectiveness and perceived support are of greater influence.[6]

MS is more prevalent in northern than in southern countries. People who moved house as children from a northern country to a southern one have a lower risk of contracting MS than those they left behind. This difference has not been found amongst post-pubertal children, however.

Although MS mostly occurs in young adults, there is also a variant with childhood onset. On average, it takes decades before the disease causes serious disability; amongst children with MS it may take even longer.[7]

The risk of contracting MS without vaccination is not well known in the Netherlands. In a research study carried out in the province of Groningen, which was published in 1985, over two new cases of MS per 100 000 people were detected every year for a period of 20 years.[8] As far as the committee has been able to determine this study provides the only data available on incidence – the frequency of new cases – in the Netherlands.

2.3 Earlier findings on vaccination against hepatitis B and MS

In 2001 the Health Council discussed the possibility of a link between hepatitis B vaccination and MS, in an advisory report on the general vaccination of infant children against hepatitis B.[9] This was because in the early 1990s French research had linked MS in individual patients with hepatitis B vaccination.

The onset of MS in someone who has been vaccinated against hepatitis B is not in itself unusual, as MS appears with a certain frequency amongst all young adults. In other words, we may expect this combination to appear with a certain statistical regularity. However, numerous specific research studies have failed to find any causal links between the two.[10-19]

On the basis of these research results the Health Council concluded in 2001 that there were no indications that the hepatitis B vaccine caused MS.

Chapter 3

Evaluation of new findings

3.1 New research results

In 2004 Hernán and his colleagues published the results of a case-control study using data taken from the UK's General Practice Research Database (GPRD), a database of medical details from family practitioners.

Their most important finding was an odds ratio (relative risk) of 3.1 (95 percent confidence interval 1.5-6.3) for the onset of MS symptoms within three years of a hepatitis B vaccination; in other words, the likelihood of a person contracting MS within three years of a vaccination was three times higher than if they had not been vaccinated. The study found no statistical link between MS and vaccination against influenza or tetanus.[20]

The study therefore suggested a link. At the same time the data made it clear that even if such a link existed, vaccination was by no means the most important factor in the onset of MS; 93 percent of the MS patients in the study had not been vaccinated against hepatitis B. Just as in the Netherlands, in the UK hepatitis B vaccination is generally given to people from specific high-risk groups.

The question, then, is whether Hernán's research results are entirely convincing. In order to answer this question, the committee will examine its methodological quality and compare its outcomes with those from other research. This will also make use of the updated systematic review that was prepared by Jefferson and colleagues at the Health Council's request. The committee will then examine whether a plausible hypothesis can be advanced to explain a possible link

between hepatitis B vaccination and MS, since this is also relevant to the judgement on the probability of such an association.

3.2 The evidential value of Hernán's research

Was observational research the correct choice?

Hernán's research study was observational; that is to say, use was made of situations that occurred in daily practice. This meant that it was external circumstance, not the research design, which determined whether someone was vaccinated against hepatitis B. Observational research therefore has a lower evidential value than does experimental clinical research, in which it is the researchers who decide who is to be exposed to the intervention under investigation. Ideally, such research is carried out according to a 'double blind' design in which neither patient nor researcher know who actually receives the intervention under investigation and who receives the comparable intervention. In observational research the findings can also be distorted by other (risk) factors, which may not be known.

However, it is not always feasible to carry out experimental research. That is also the case here: an experimental research study into the question of whether the risk of contracting MS is raised after vaccination against hepatitis B would have to comprise hundreds of thousands of participants.

The committee therefore considers that Hernán's choice for observational research was correct. However, it does mean that finding a link between hepatitis B vaccination and MS does not furnish proof of a causal relationship between them; another research study would be needed to establish such a causal link. Hernán and his colleagues say the same.[20,21]

Was the study well designed?

In order to examine whether Hernán and his colleagues' findings could be attributed to shortcomings in the design or the execution of their study, or to bias caused by other (risk) factors, the committee provides a brief summary of the methods which this research study employed.

The study was set up as a case-control study using the GPRD database, which tracks the demographic, illness and treatment aspects of 3 million Britons. The participating general practitioners (GPs) are specially trained to record their patient data in a standardised way. This database was set up for the purposes of

research, and in the committee's opinion it is suited for research into the safety of medicines, including vaccines.

In a case-control study, the degree of exposure to a suspected risk factor is compared between a number of patients having the illness concerned and a number of control subjects. In the GPRD database, Hernán and his colleagues identified all patients with the illness code for MS. They then asked the GPs for copies of all MS-related consultations, referrals, test results and hospital records. Two researchers, who did not have access to the hepatitis B vaccination data, worked independently of each other to assess whether the patients met the criteria for Poser's diagnosis of MS. As index dates for two separate analyses, the researchers chose 1) the earliest date at which symptoms appeared which later transpired to indicate MS, and 2) the date of the actual MS diagnosis. The analysis selected only those patients for whom the GPRD held background data going back for an uninterrupted period of at least three years before the appearance of the first symptoms of MS.

For each MS patient, 10 matched control subjects were randomly selected. Here, too, only those patients were selected for whom the GPRD held background data going back at least three years before the appearance of the first symptoms of MS in the corresponding MS patient.

For both the MS patients and the control subjects, data on hepatitis B vaccinations were taken from the treatment details held in the GPRD.

Of the original 713 MS patients, 163 thereby qualified for analysis (11 with, and 153 without hepatitis B vaccination). These were compared with 1,604 control subjects (39 with, and 1,565 without hepatitis B vaccination).

Both the World Health Organisation (WHO) and the American Centers for Disease Control and Prevention (CDC) have argued that these numbers are too small to warrant firm conclusions.[22,23]

In the committee's view, the selection of patients and control subjects is clearly described in the article and carefully carried out. In the selection of patients, use was made of generally accepted criteria for the diagnosis of MS. The link the researchers found between hepatitis B vaccination and MS is statistically significant according to the usual criteria. In the committee's view, the way patients and control subjects were selected and their low numbers do not in themselves cast any doubt on the reliability of the study's findings. The French *Commission Nationale de Pharmacovigilance* also judged that Hernán and his colleagues designed and executed their study in a suitable way.[24]

However, the group under study does suffer from a clear limitation. The GPRD is considered to be representative for the general population of England and Wales. As in the Netherlands, in the UK hepatitis B vaccination is usually

administered to people from specific high-risk groups. It cannot be ruled out that the link Hernán found between vaccination and MS can be explained by a link between these risk groups and MS, independently of the vaccination. Furthermore, Hernán's research group is formed almost exclusively of adult MS patients, and therefore furnishes no information about a possible link between hepatitis B vaccination and MS in infants and young children. MS occurs very rarely in these age groups, and less frequently than the national average. The limited size of the research group means that it is unclear whether Hernán's findings can be generalised to include children and people without specific risks for hepatitis B.

Is there any information bias?

In designing their research, Hernán and his colleagues went to considerable lengths to avoid bias caused by other (risk) factors. According to the WHO, however, a possible explanation for the findings could lie in a misclassification of the vaccination status. Minimal differences between patients and control subjects in the way their vaccination details were obtained might lead to different conclusions.[22] Nevertheless, the committee sees no indications of this; the vaccination details were obtained identically for MS patients and control subjects on the basis of a database that was already in existence.

The chosen research design also means that there can be no question of the research question having influenced the data. Such an influence on the results is only conceivable if, independently of this research and in advance of it, doctors or patients had suspected a link with hepatitis B vaccination at the moment of diagnosis with MS and had added selective vaccination data to the dossier as a result. There are no indications that this took place.

It is possible, however, that the GPs who served as data source in this study were not always aware of their patients' vaccination status or MS diagnosis. For instance, health workers may have been vaccinated at their own workplaces, or their MS-related complaints may have resulted in specialist diagnosis and treatment through workplace contacts. If this were the case, a possible link may have been underestimated or even overlooked.

The committee concludes that it is unlikely that Hernán's findings can be explained by information bias.

May bias have been caused by other (risk) factors?

There is another issue worth discussing at this point. In the UK, as in the Netherlands, it is principally people from specific high-risk groups who are vaccinated against hepatitis B. It is possible that people from specific high-risk groups for hepatitis B also have higher than average risk factors for MS. If this is the case, it would introduce a bias in the study results. Although the possibility cannot be discounted altogether, it is unlikely that the findings have been biased by other risk factors; so far only a few risk factors have been found for MS (see section 2.2), and none of these correspond to risk factors for HBV infection.

Similarly, it is conceivable that people in high-risk groups for hepatitis B might seek treatment for other medical complaints more often or more quickly than others. In that case, the study would incorrectly suggest a link between hepatitis B vaccination and MS (the problem of 'confounding by indication'). There are no indications that such is the case in this study, but the possibility cannot be excluded.

The role of chance

Finally, the possibility cannot be excluded that the findings are the result of chance. The statistical methods employed mean that about one in twenty of such studies will detect a link entirely by chance even though no such link exists.

The judgement of the committee

In 2001 the Health Council discussed the possibility of a link between hepatitis B vaccination and MS. A number of specific research studies subsequently failed to substantiate this link. In 2004 the possibility of a link was raised again, this time by the publication of the research carried out by Hernán and his colleagues. The committee has now evaluated the quality Hernán's research; what is its opinion?

Hernán's research was carried out *lege artis*. In their research, Hernán and his colleagues assumed that the MS diagnoses had been established according to objective criteria. The researchers examined the link between hepatitis B vaccination and the later onset of MS with particular care. Unlike most other research studies in this field, they based their index dates on the moment that people first consulted their family doctor with MS-related complaints. Again, unlike most other research studies in this field, they employed a follow-up period of at least three years. For these reasons it is improbable that the team's findings can be attributed to shortcomings in the design or execution of their research. However,

the study concerns observational research that as such cannot furnish proof of a causal relationship between hepatitis B vaccination and MS. Its careful design means that its results cannot be dismissed, however. The research is a signal that closer investigation needs to be carried out.

3.3 The evidential value of pooled research

In order to be better able to compare the research carried out by Hernán and his colleagues with the results of other published research, the Health Council commissioned Jefferson and his colleagues to update the systematic review of this research they published in 2003.[25] This update is available as Appendix D.

According to Jefferson and his colleagues, the available research suffers from too many methodological shortcomings to provide more than limited insight into a possible relationship between hepatitis B vaccination and MS; for instance, only three of these research studies employed clearly defined criteria for the diagnosis of MS: besides the study carried out by Hernán, these were studies by Acherio and colleagues (in 2001) and by DeStefano and colleagues (in 2003).[11,19,20] Furthermore, not one of the studies gave details of the moment at which complaints had first been presented to the doctor, as Hernán had done; this made it impossible to pool research into the link between vaccination and the later onset of related complaints.

Where it did prove possible to pool the results of these studies, including Hernán's, no significant link was found between hepatitis B vaccination and demyelinising disease, optic neuritis (inflammation of the optic nerve), or multiple sclerosis occurring two years or later thereafter.

As before, the updated systematic review of scientific research furnished the researchers with no proof that a causal link exists between hepatitis B vaccination and the later onset of demyelinisation syndromes in general or MS in particular.

The judgement of the committee

Pooled research gives no indications for a link between hepatitis B vaccination and MS.

3.4 The plausibility of a causal relationship

The committee has considered the question of whether a plausible explanation could be given for a possible link between vaccination with the recombinant hep-

atitis B vaccine and the later onset of multiple sclerosis. The scientific literature has suggested that identical amino acid sequences occur in an enzyme of the hepatitis B virus, the HB virus polymerase (HB-pol), and the myelin sheath of nerves. It is conceivable that such a correspondence might induce an autoimmune process in susceptible individuals.[26-30] Such a mechanism is termed 'molecular mimicry'.

Jefferson and his colleagues had also noted in their systematic review that molecular mimicry has been reported between parts of the hepatitis B virus and the myelin sheath of nerves, and it is on these grounds that they argue that molecular mimicry forms a plausible explanation for a possible link between hepatitis B vaccination and multiple sclerosis.

HB-pol forms no part of recombinant vaccine, however; if it were present at all, it could only be in the form of a trace contamination. It is therefore extremely unlikely that recombinant vaccine would provoke an autoimmune reaction. The occurrence of molecular mimicry partly depends on genetic factors in the host, and this dependence on genetic factors means that autoimmunity is an extremely rare phenomenon.

The committee notes here that the clinical relevance of these identical amino acid sequences also remains uncertain. Identical amino acid sequences are found relatively frequently, without this correspondence having any clinical relevance. Clinical relevance would require that the immune system of a susceptible person recognised these identical amino acid sequences as such, and cross-reacted with the body's own antigen. In order to determine the clinical relevance of molecular mimicry in this case, research would have to be carried out amongst susceptible test animals; this kind of research has not been carried out in this case.

HB-pol does form a part of the hepatitis B virus itself, and is found in relatively high concentrations in people with an active HBV infection. Countries such as the UK (and the Netherlands) vaccinate precisely those people who run a raised risk of infection. In these countries, vaccinated people therefore have a higher likelihood of coming into contact with the virus and becoming infected. This may explain the statistical link that Hernán found between vaccination and MS; the link would then actually be a link between infection with the hepatitis B virus and MS, and the apparent link with vaccination would arise because precisely those people running the greatest risk of catching the disease would be selected for vaccination against it: the problem known as 'confounding by indication'. Incidentally, hepatitis B itself has never been associated with MS in the scientific literature.[26]

The judgement of the committee

In the opinion of the committee, molecular mimicry does not form a logical, causal explanation for a possible link between hepatitis B vaccination and MS. Molecular mimicry might, however, underlie a possible link between infection with the hepatitis B virus and the onset of MS. However, the committee has found no indications of this in the scientific literature.

3.5 Follow-up research

Following the publication of Hernán's research results, follow-up research was carried out in France by Mikaeloff and colleagues. As had been the case for Hernán, this was a case-control study, in which the vaccination anamnesis was compared in 143 MS patients and 1,122 control subjects with no MS. In contrast to Hernán's study, this study looked at children below the age of 16. MS patients were selected from the KIDSEP cohort* that includes most incident cases of patients with childhood-onset MS in France. The control subjects were taken from a random sample of the general population and were matched by age, sex and geographic location.

Mikaeloff and his colleagues took as their starting point patients who had been diagnosed as having MS using objective criteria. As in Hernán's study, they based their data on exposure to vaccination on pre-prepared and collated sources, in this case vaccination booklets. The statistical analysis of the data was broadly in line with that carried out by Hernán. As with Hernán, the statistical analysis of the link between hepatitis B vaccination and the later onset of MS concerned a period of three years after exposure, but this time shorter and longer periods after exposure were also examined. None of these analyses found any indications for a link between hepatitis B vaccination and MS: an equally large proportion of MS patients and control subjects (32 percent) had been vaccinated against hepatitis B.[31]

An important difference between Mikaeloff's and Hernán's studies, and an advantage of Mikaeloff's, is that Mikaeloff's concerned children. Moreover, and unlike the participants in Hernán's study, the participants in Mikaeloff's study were not members of a risk group for HBV infection. For this reason the risk of 'confounding by indication' is probably much smaller in Mikaeloff's study than it is in Hernán's study.

* Kid Sclérose en Plaques

The judgement of the committee

In the opinion of the committee, the research carried out by Mikaeloff and his colleagues is broadly characterised by the same careful design and analysis as that of Hernán. An important advantage of Mikaeloff's study is that it concerned children. The results of this research give no indication of a link between vaccination with recombinant hepatitis B vaccine and MS.

3.6 Conclusion

The committee has evaluated the evidential value of the research carried out by Hernán and his colleagues. What is the committee's judgement?

The research was carried out *lege artis*. However, it concerned an observational research study that as such cannot furnish proof for a causal link between hepatitis B vaccination and MS.

In order to better compare the research work done by Hernán and his colleagues with the results of other research studies, the Health Council commissioned an updated systematic review of the epidemiological research that has been carried out into the link between hepatitis B vaccination and MS. The pooled research gave no indications for a link between hepatitis B vaccination and MS.

In the committee's opinion, molecular mimicry forms no logical, causal explanation for a possible link between hepatitis B vaccination and MS. The research carried out by Mikaeloff and his colleagues also found no indications for a link between vaccination using recombinant hepatitis B vaccine and MS.

On the basis of the available data, the committee concludes that a link between vaccination with recombinant hepatitis B vaccine and MS is improbable.

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Bijlage **D**

Hepatitis B (HB) Immunization and Onset of Demyelinating Disease

Systematic Review of the Evidence

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Index

Abstract

Objective

To assess evidence of a possible association between exposure to vaccines against Hepatitis B (HB) and onset of Demyelinating Disease (DD) (Multiple sclerosis MS and/or optic neuritis ON).

Design

Systematic review and meta-analysis of the evidence.

Methods

We searched the Cochrane Library, MEDLINE, Current Contents, Cinhal, Embase, Gateway Mesh (from 1979 to June 2002) and The Cochrane Library, MEDLINE, EMBASE, Pub Med (from June 2002 to June 2006) in any language and contacted manufacturers and corresponding authors. We included non randomised comparative studies assessing exposure to HB vaccines and DD. Whenever possible we carried out a meta-analysis and expressed risk as odds ratios or risk ratios. Due to inconsistent and non-standardised reporting we carried out sub-analyses only by time from exposure to onset of DD.

Results

We included 13 studies (7 case- controls, 1 case- crossover, 1 cohort and 4 ecological studies) of relatively poor quality. Our comparisons failed to reach statistical significance. However, analysis within 2 months and 0-12 months of vaccination yielded high odds ratios (OR 1.63, 95% confidence intervals 0.82 to 3.23 - 748 observations – for DD and OR 1.76 95% confidence intervals 0.86 to 3.61 - 2227 observations – for MS respectively).

Conclusion

We found no evidence of an association between vaccines and HB and the onset of any of the demyelinating syndromes. However because of poor methodological quality and the presence of a plausible causal hypothesis such an association cannot be discounted.

Background

Hepatitis B

Hepatitis B is a disease of the liver caused by hepatitis B virus (HBV), a DNA virus (hepadnaviridae class).

The virus contains numerous antigenic components, including HBsAg, hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg). The virus contains partially double-stranded DNA, and a DNA-dependent DNA polymerase enzyme (HBpol). HB virus is relatively resilient and, in some instances, has been shown to remain infectious on environmental surfaces for at least a month at room temperature (a1).

More than two billion people world wide have evidence of past or current HBV infection and 350 million (prevalence 2 %) are chronic HBV carriers. Three quarters of the world's population live in areas where there are high levels of infection (a2).

Infection usually occurs in early childhood, is often asymptomatic and can lead to chronic carrier state.

About 25% of carriers (one million people a year) die from chronic active hepatitis, cirrhosis or primary liver cancer.

It is estimated that HBV causes 60 to 80 % of the world's primary liver cancer, one of the three top causes of cancer deaths in males in East and South-East Asia, the Pacific basin and sub-Saharan Africa.

HBV virus is transmitted by percutaneus or permucosal exposure to infectious body fluids, by sexual contacts with infected person and perinatally from infected mothers to infants. No animal or insect hosts or vectors are known to exist.

The consequences of acute HBV virus infection are highly variable. The incubation period ranges from 6 weeks to 6 months, (average, 120 days), and the development of clinical manifestations is highly age-dependent (a3). Newborns generally do not develop any signs or symptoms, only 5 to 15 % of children aged

one to five are symptomatic and 33 to 50 % of infected older children and adults are symptomatic.

The clinical course of acute hepatitis B is indistinguishable from that of other types of acute viral hepatitis. Clinical signs include anorexia, nausea, malaise, vomiting, jaundice, dark urine, clay-coloured or light stools, and abdominal pain. aspecific extra-hepatic symptoms such as rashes, arthralgia, and arthritis occasionally occur. Jaundice may persist for days or weeks. Fulminant hepatitis occurs in approximately 1 to 2 % of people with acute disease, with a case-fatality ratio of 63:100 to 93:100. Most acute HBV virus infections in adults result in complete recovery with elimination of HBsAg from the blood and the production of anti-HBs creating immunity from future infection.

Clinical signs and symptoms occur more often in adults than in infants or children, who usually have an asymptomatic acute course. However, approximately 50% of adults who have acute infections are asymptomatic. Approximately 10% of all acute HBV infections progress to chronic infection, with the risk of chronic HBV virus infection decreasing with age.

Persons with chronic infection are often asymptomatic and may not be aware that they are infected, yet are capable of infecting others. Chronic infection is responsible for most HBV-related morbidity and mortality, including chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma. Chronic active hepatitis develops in over 25% of carriers, and often results in cirrhosis.

The frequency of HBV infection and patterns of HBV transmission vary markedly among different parts of the world. Approximately 45% of the world's population live in areas where the prevalence of chronic HBV infection is high (i.e. at least 8% of the population is HbsAg-positive); 43% live in areas where the prevalence is moderate (i.e., at least 2-7 % of the population is HbsAg-positive) and 12% live in areas of low endemicity (i.e. less than 2 % of the population is HbsAg-positive).

Areas of high endemicity include most of Asia (except Japan and India), most of the Middle East, the Amazon basin, most Pacific Island groups, Africa and other populations such as Australian aborigines and Maoris in New Zealand.

The vaccines

HBV vaccines have been commercially available since 1982 and are composed of highly purified preparations of HbsAg, a glycoprotein of the outer envelope of HBV, that is also found in the serum of people with acute or chronic infection.

Vaccine can be prepared harvesting HbsAg from the plasma of people infected with chronic infection (plasma-derived vaccine – PDV) or by inducing some cells to express a viral protein (recombinant DNA vaccine – yeast derived vaccine – YDV). Currently some HBV vaccines are combined with DPT, Hib and IPV.

PDVs are no longer produced in USA or in Western Europe, but are still produced in Asia. The use of PDVs was limited by fears regarding the safety of plasma-derived products and the high costs of vaccination. YDVs are produced by inserting plasmids containing HbsAg genes (226-amino-acid S gene or 281-amino-acid preS2 + S gene), into yeast or mammalian cells. The expressed HbsAg polypeptides self-assemble into immunogenic spherical particles closely resembling natural 22-nm particles found in the serum of people with chronic HBV infection.

The vaccines undergo various inactivation steps and are highly purified. For yeast derived vaccine purification is done by separation techniques such as chromatography and filtration.

Commonly aluminium phosphate or aluminium hydroxide is added to the vaccine as adjuvant. Thimerosal is commonly used as a preservative (a3).

In 1987 the WHO Hepatitis Technical Advisory Group recommended integration of HBV vaccine into the Expanded Programme on Immunisation (EPI). Since then, a number of other WHO expert groups have endorsed this recommendation and in 1992 the World Health Assembly approved the target of introducing HBV vaccine in countries with carrier prevalence of 8 % or greater by 1995 and in every country by 1997 (a4).

With the launching of the Accelerated Vaccine Introduction Priority Programme under the Vaccines and Biological and with the support of GAVI to those countries that hitherto could not purchase the vaccine, the introduction of this vaccine has now accelerated significantly.

As of December 2000, 130 countries with significant hepatitis disease burden and a robust immunization system have introduced hepatitis B vaccine into their routine immunization programmes. The 130 countries that introduced hepatitis B vaccine represent 66% of the total of 193 countries, accounting for approximately 47% of the surviving birth cohort world-wide and for approximately 64% of the persons with chronic HBV infections world wide (a5).

The efficacy of hepatitis B vaccine has been demonstrated in clinical trials involving several high risk groups, including homosexual men, healthcare workers, haemodialysis staff members, children living in areas of high endemicity, and infants of HbsAg-positive (highly infectious) mothers (a3). These studies demonstrates the overall efficacy of 85 to 95% and virtually complete protection among people who developed antiHBs titres greater than 10 mIU following vaccination.

The effectiveness of hepatitis B vaccination programs has been evaluated by the surveillance of acute disease, and by population based serological studies, because most HBV infection in children are asymptomatic (a3).

Despite the administration of hundreds of millions of doses and an apparently good safety record in trials, in the last decades several associations between exposure to HBV vaccines and rare events have been hypothesized (a6)(a7)(a8)(a9)(a10), including:

a hair loss
b fever and suspected sepsis in newborns
c multiple sclerosis and other demyelinating disorders
d risk of type I (juvenile) diabetes
e neonatal mortality
f systemic lupus erythematosus, rheumatoid arthritis and other autoimmune disorders
g chronic fatigue syndrome
h ataxia
i wheezing and asthma
j arthritis
k subdural haematoma or intracranial haemorrhage

Evidence assessing the likelihood of these association was the focus of the 2002 version of the review. Our review concluded that available evidence was insuffi-

cient to accept or reject the various hypotheses. For the 2006 update we will concentrate on the alleged association with demyelinating disease.

Rationale for the 2002 review and its update

The burden of HB disease and its potential seriousness are reflected in widespread immunisation programmes and on the extended EPI status of HB vaccines. Questions on the safety of HB vaccines may undermine confidence in the programme, reducing compliance and diminishing chances of controlling the disease.

In the 2002 review, available evidence was inconclusive because its quantity was insufficient but also because important caveats related to the quality of the studies needed to be taken into account.

A number of methodological problems required addressing systematically:

a) The study designs used to evaluate the association between vaccines and adverse events are diverse and our knowledge of their ability to contribute in assessing vaccine safety needs clarification, particularly in view of the possible impact of poor quality design on the evaluation of causality.
b) The issue of vaccine safety has rarely been evaluated systematically and prospectively; most of the available studies were aimed at investigating individual hypotheses and it is possible that the data collected in a study contain information relevant to other hypotheses that are lost because the focus of the study disregards them.
c) A publication bias may also be present when studies with notable or confirmatory results are published, leaving studies with unexpected or inconclusive findings unpublished. The results of an exploratory review of case-control studies assessing the evidence of the link between HBV vaccination and multiple sclerosis show that an inverse publication bias is also possible and that the negative studies are more likely to be published (a11).
d) Information on the links between vaccines and rare and serious outcomes are also likely to be contained in studies aimed at exploring aspects other then vaccine safety. Their identification and retrieval requires appropriate and sensitive search methods.
e) The lack of controls truly unexposed to HB vaccines or any other vaccines which may affect the outcome in question makes drawing conclusions perilous. The variety of retrospective study designs used in the evaluations is a direct consequence of the absence of unexposed controls.

These problems seriously affect the possibility of making the best use of the available knowledge and limit the credibility and the rationality of decision making in this field.

An available tool to try to overcome these problems is the application of systematic reviewing to the issue of vaccine safety.

This requires adaptation of many of the principles of this method, particularly regarding search strategies and the quality assessment of non-experimental study designs.

The 2002 review applied this approach to the evidence of safety of vaccines against HBV. However, since the publication of our review more studies have been published and a immunological causal model has been proposed.

According to the proposed model, contamination of both PDV and YDV with fragments of HB pol can lead through a process of molecular mimicry to a cross reaction between HB pol antigens and myelin surface protein.

Although the length of latency is unspecified, the finding that HB pol and human myelin share several aminoacid sequences makes the hypothesis very plausible (a12, a13).

Objectives

To identify, retrieve, assess and assemble available evidence on the frequency of demyelinating events associated with HBV vaccines.

Criteria for considering studies for this review

Types of studies

We considered all comparative prospective or retrospective studies of a design listed in Appendix A regardless of language.

Studies had to be carried out in the period 1979-2006 (1979 is thought to be the year of possible publication of the first HBV vaccine safety study).

Types of participants

Healthy individuals or people with demyelinating diseases.

Types of interventions

Vaccination with any HBV vaccine, in any combination, dosage, preparation or time schedule.

Types of outcome measures

The number and type of demyelinating events observed following HBV vaccination.

Search strategy for identification of studies

For the 2002 review we performed two search strategies: the original protocol strategy based on study design and an additional search based on a list of potential adverse events. The searches were carried out on the following databases: Cochrane Library, MEDLINE, Current Contents, Cinhal, Embase, Gateway Mesh.

The Cochrane Library was searched to identify reports of randomized and quasi-randomized controlled trials (CENTRAL/Cochrane Controlled Trials Register) and published reviews (Cochrane Database of Systematic Reviews, NHS Database of Abstracts of Reviews of Effectiveness). Searching the Cochrane Library also included identifying reports from the handsearch of the journal Vaccine.

MEDLINE was searched from 1979 to June 2002 using the following search strategies:

Study Design based strategy:

1 Search hepatitis b vaccine* Field: Title/Abstract Word
2 Search hepatitis b vaccines[MeSH Terms] OR hepatitis b vaccines / adverse events[MeSH Terms] OR hepatitis b vaccines / contraindications[MeSH Terms] OR hepatitis b vaccines / poisoning[MeSH Terms]
3 Search # 1 OR #2
4 Search safety[MeSH Terms] OR safety[Title/Abstract Word]
5 Search "adverse events" OR "possible link" OR "risk assessment" OR reactogenicity OR tolerability Field: Text Word
6 Search # 4 OR # 5
7 Search # 3 AND # 6
8 Search randomized controlled trial OR clinical trial OR controlled clinical trials Field: Publication Type
9 Search randomized controlled trials OR controlled clinical trials OR clinical trials Field: MeSH Terms
10 Search random allocation OR double-blind method OR single-blind method Field: MeSH Terms
11 Search cross-over studies OR placebos OR research design OR comparative studies OR case-control studies OR cohort studies OR follow-up studies Field: MeSH Terms
12 Search "clinical trials" OR placebo OR random Field: Text Word

13 Search cohort OR prospective OR follow-up Field: Title/Abstract Word
14 Search # 8 OR # 9 OR # 10 OR # 11 OR # 12 OR 13
15 Search # 7 and # 14

Adverse Events based strategy:
1 Search hepatitis b vaccine* [Title/Abstract] OR hepatitis b vaccine [MESH] OR “hepatitis b vaccines/adverse effects [MESH] OR “hepatitis b vaccines/contraindications”[MESH] OR “hepatitis b vaccines/poisoning”[MESH]
2 Search safety[MESH Terms] OR safety[Title/Abstract]
3 Search “adverse event* ”[Title/Abstract] OR “possible link”[Title/Abstract] OR “risk assessment”[Title/Abstract] OR reactogenicity [Title/Abstract] OR tolerability[title/Abstract]
4 Search # 2 OR # 3
5 Search # 1 AND # 4

EMBASE from 1979 to June 2002, Biological Abstracts from 1979 to June 2002 and Science Citation Index from 1974 to June 2002, were searched using search terms equivalent to the MEDLINE strategy (see above).

Bibliographies of all relevant articles obtained and any published reviews were assessed in order to identify additional studies.

Vaccine manufacturers, companies that market the vaccines, first or corresponding authors of included studies, researchers or experts in the field were also contacted to identify further unpublished studies.

To retrieve as many unpublished data as possible, we contacted the following vaccine manufacturers:
1 Glaxo SmithKline Biologicals, Belgium.
2 Centre for Genetic Engineering and Biothechnology (CIGB), Cuba
3 National de Biopreparados, Cuba
4 Labiofarm, Cuba
5 Aventis Pasteur Serums and Vaccines, France
6 Mitsubishi Chemical Corporation, Japan
7 The Chemo-Sero-Therapeutic Research Institute, Japan
8 The Green Cross Corporation, Japan
9 The Research Foundation for Microbial Disease of Osaka University, Japan
10 Dong Shin Pharmaceuticals Co Ltd, Korea
11 Swiss-Serum Institute, Switzerland

For the 2006 update we searched PubMed, EMBASE and the Cochrane Library 2006 issue 2 as follows:

PubMed
#1 "Hepatitis B Vaccines"[MeSH]
#2 "hepatitis b"[All Fields]
#3 (vaccin*[Title/Abstract] OR immuni*[Title/Abstract] OR inoculat*[Title/Abstract])
#4 # 2 AND # 3
#5 # 1 OR # 4
#6 "Demyelinating Diseases"[MeSH] OR "Optic Neuritis"[MeSH]
#7 "multiple sclerosis"[All Fields] OR optic neuritis OR "demyelinating"[All Fields] OR "myelitis"[All Fields] OR "encephalomyelitis"[All Fields]
#8 # 6 OR # 7
#9 # 8 AND # 5

Embase:
#1 'hepatitis b vaccine'/exp
#5 'hepatitis b':ti,ab
#6 vaccin*:ab,ti OR immuni*:ab,ti OR inoculat*:ab,ti
#7 # 5 AND # 6
#8 # 1 OR # 7
#9 'demyelinating disease'/exp
#10 'optic neuritis'/exp
#11 'retrobulbar optic neuropathy'/exp
#13'multiple sclerosis':ab,ti OR 'optic neuritis':ab,
ti OR demyelinating:ab,ti OR myelitis:ab,ti OR enc ephalomyelitis:ab,ti
#14'multiple sclerosis'/exp/dm_si/mj OR 'multiple sclerosis'
#15'optic neuritis'/exp/mj OR 'optic neuritis'
#16'myelitis'/exp/mj OR 'myelitis'
#17'encephalomyelitis'/exp/mj OR 'encephalomyelitis'
#18# 9 OR # 10 OR # 11 OR # 13 OR # 14 OR # 15 OR # 16 OR # 17
#19# 8 AND # 18 AND [humans]/lim AND [embase]/lim

Cochrane Library:
#1 MeSH descriptor hepatitis b vaccines explode all trees
#2 "hepatitis b" in All Text
#3 (vaccin* or immuni* or inoculat*)
#4 (# 2 and # 3)

#5 (# 1 or # 4)
#6 MeSH descriptor Demyelinating Diseases explode all trees
#7 MeSH descriptor Optic Neuritis explode all trees
#8 "multiple sclerosis" in All Text
#9 "optic neuritis" in All Text
#10demyelinating in All Text
#11myelitis in All Text
#12encephalomyelitis in All Text
#13(# 6 or # 7 or # 8 or # 9 or # 10 or # 11 or # 12)
#14(# 5 and # 13)

Corresponding authors of identified studies were contacted if necessary to provide additional information.

Methods of the review

Inclusion of studies

Inclusion criteria were applied to all identified and retrieved articles independently by two reviewers.

Assessment of methodological quality

Quality assessment of non-randomised studies was made in relation to the presence of potential confounders, which could make interpretation of the results difficult. However, because of insufficient empirical evidence to demonstrate the validity of the non-randomised quality assessment screens, we used methodological quality of included studies as an aid to interpreting data.

We assessed quality of non-randomised studies in relation to the presence of potential confounders using the appropriate Newcastle-Ottawa Scales (NOS) (a14) for cohort and case control studies, and other scales (reported in Appendix B) for other non-randomised comparative study designs. For case-only design studies, we used a classification and an unpublished methodological quality checklist developed by Farrington and Jefferson and adapted from a paper by Farrington (a15).

We assigned risk of bias categories on the basis of the number of methodological items in the scales judged inadequate in each study:

low risk of bias – up to 1 inadequate item;
medium risk of bias – up to 3 inadequate items;
high risk of bias – more than 3 inadequate items;
very high risk of bias – when there was no description of methods.

Aggregation of data was dependent on the sensitivity and homogeneity of definitions of adverse events used.

Data extraction

Data extraction was performed independently by the two reviewers using a standard Cochrane Vaccines Field data abstraction form. Authors of studies were

contacted when data were insufficient or missing. Data were checked before dual loading onto RevMan software.

Data analysis

The studies were assessed for clinical homogeneity to see if the individual studies (within each design category) appeared clinically homogeneous. Basic data manipulation was carried out to calculate person-time from observed numbers of cases and incidence rates for ecological studies. For case-control studies when data in tabular form were not available, the numerators of case and controls were derived from the odds ratio (OR) and its confidence interval (a16).

Likely causes of between-study heterogeneity of effect estimates are different study designs, methodological quality, age groups, periods of follow-up and possible event latency, risk profile, socio-economic class, types of vaccines, schedules, demyelinating event definition and source of funding. Whenever possible we presented analyses or data sets stratified accordingly. Statistical heterogeneity was explored, using the Cochran's Heterogeneity Q statistic and I^2 statistics (a17, a18). The I^2 statistic [a17 a18] was calculated for each pooled estimate, in order to assess the impact on statistical heterogeneity. I^2 may be interpreted as the proportion of total variation among effect estimates that is due to heterogeneity rather than sampling error, and it is intrinsically independent of the number of studies. When $I^2<30\%$ there is little concern about statistical heterogeneity [a17,a18]. When significant heterogeneity was found, sensitivity analysis was performed and a meta-analysis of these studies carried out within each group category using the random effect model (DerSimonian and Laird method,a19).

Where studies were found to be homogenous, a meta-analysis of the studies were carried out within each design category using fixed effect model (Mantel – Haenszel method). Pooled ORs were calculated when more than one study could be included in the meta-analysis. Point estimates were expressed as ORs for case-control and case cross-over studies and as Rate Ratios for case-only studies. Study results were described individually in the descriptive tabular format of the review (a20).

Results of the review

Identification of studies

The flow of identified studies is shown in Figure 1. We excluded 44 articles after retrieval. The most common reason for exclusion was not providing any original data (29 papers, or 66%). We included 7 case-control studies (1-7), 1 case-cross over study (8), 1 cohort study (9) and 4 ecological studies (10-13).

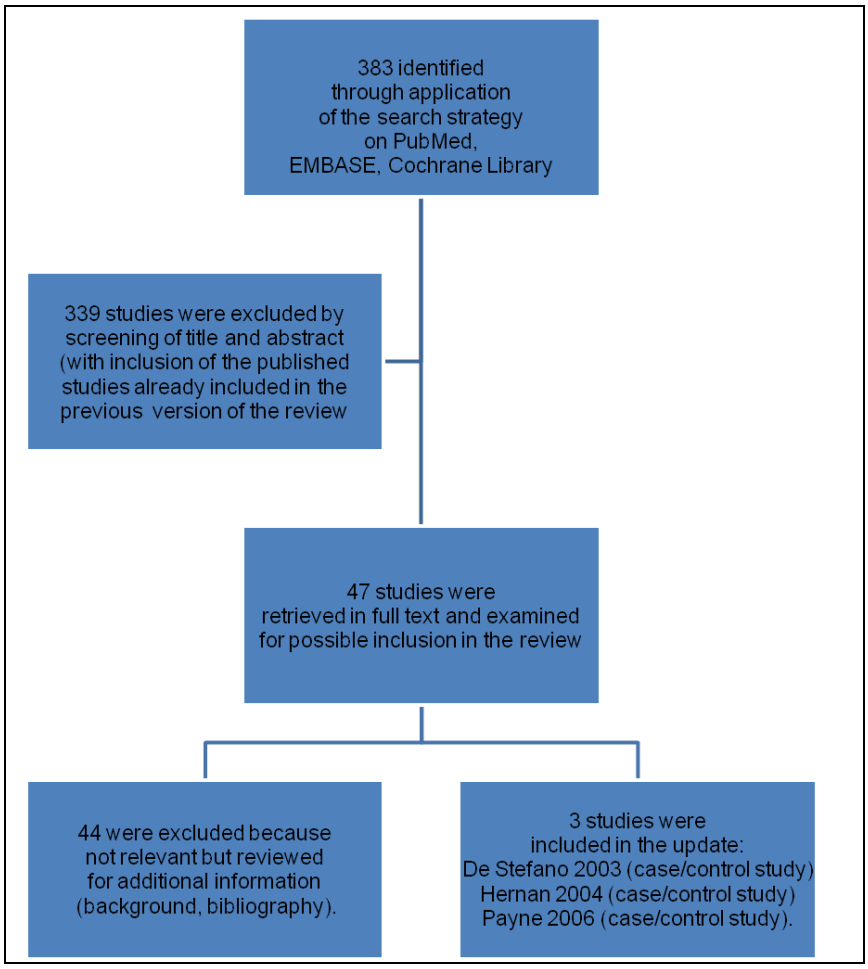

Figure 1 Identified studies.

Two case-control studies were respectively notes and slides from a presentation (1) and an unpublished manuscript (4). Included studies are described in Table 1.

Table 1 Description of included studies by design.

Case-Control				
Study and Reference	Participants	Cases and Controls	Exposure	Notes
Payne DC *et al. Anthrax vaccination and risk of optic neuritis in the United States military, 1998-2003.* Arch Neurol 2006 ; 63 (6): 871-5.	US military personnel aged at least 18 yrs.	Cases (n = 1131) : Subjects having a diagnosis of optic neuritis (ON) between 1.1.1998 and 31.12.2003. The following ICD-9 codes were considered : 377.30-32, 377.39. Controls (n = 4524) : subjects were matched to the cases on the basis of sex, deployment during the 18 weeks before diagnosis, military component. The study was carried out by using data from the Defense Medical Surveillance System, a longitudinal surveillance database.	Date of case diagnosis was ascertained and immunisation status (Anthrax, smallpox, Hepatitis b, influenza) verified by means of electronic record in respect of three time intervals : 6, 12, 18 weeks before onset. For controls vaccination status was determined for the three interval before index date. Results were focused on the 18-week time interval.	Conclusions : No statistically significant association between immunisation with HA vac and onset of ON were observed during the considered time intervals before disease onset.
Hernàn MA *et al. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study.* Neurology 2004;63(5):838-42.	Subjects included in the General Practice Research Database (GPRD).	Cases (n=163) : Subjects with confirmed MS diagnosis, whose records were present in the GPRD at least 3 years before the first symptom of MS. Controls (n= 1604) : subjects without MS, whose records were present in the GPRD at least 3 years before the index date (date at which diagnosis of MS was confirmed for the correspondent case). Controls were matched to cases on age, sex, practice, date of joining practice.	Immunisation with HB vacc was determined by means of medical records. Cases and controls were considered vaccinated against HB if they have been immunised within 3 years before index date. Total number of immunised subject was also stratified by time interval before index date (never, 0-1 year, 1 to 2 years, 2 to 3 years) and by number of received doses (1 to 2 or at least 3).	Conclusions : Vaccination against HB was associated with a 3-fold increase of MS incidence in the 3 years following immunisation.

Ascherio, A. *et al Hepatitis B vaccination and the risk of multiple sclerosis.* N Engl J Med 2001;344(5):327-332.	Participants in the large cohorts involved in two ongoing studies.	For each woman with multiple sclerosis, were randomly selected as control five healthy women and one woman with breast cancer, which were included as control so as to address the potential bias that may derive from differential recall among women with a serious disease. They were matched to the woman with multiple sclerosis according to year of birth, study cohort, and (for the women with b.c.) date of diagnosis.	Immunization with hepatitis B vaccine assessed by means of a questionnaire and vaccination certificate within 2 years or more than 2 years before the index date.	Conclusions: No association between HBV and MS

Case-Control

Study and Reference	Participants	Cases and Controls	Exposure	Notes
De Stefano F. *et al Vaccinations and risk of central nervous system demyelinating diseases in adults.* Arch Neurol 2003; 60(4): 504 – 509.	Data from Vacine Safety Datalink	Cases : Physician diagnosis of multiple sclerosis or optic neuritis in medical record. Controls : Up to 3 controls per case were selected from automated HMO member files, at least 1 year of HMO enrollment, matched on age (within 1 year) and gender.	HB vaccination on the basis of medical records.	Conclusions: The hypothesis of an association between HBV and DD is not supported
Fourrier, A. *Pharmacovigilance and Case - control study of hepatitis B vaccine and Multiple sclerosis* (Presentation to Immunisation Safety Review Committee).	In or outpatients from 17 French departments of neurology between 1.1.94 and 31.12.95	Cases : Presented a first ever episode of CNS demyelinating diseases within the 6 months preceding the examination. 236 were included. Controls : matched to the cases by sex, age, center, date of referral. Pathologies, for which they were referred, had to not modify the probability of vaccination.	Receipt of one or more doses of HBV (telephonic interviews verified by vaccination certificates) .	Conclusions: No “strong” association between HBV and DD. A slight increase in risk cannot be excluded.
Sturkenboom MCJM *et al*. *The association between hepatitis B vaccination and multiple sclerosis or central demyelination* Pharmacoepidemiology and Drug Safety 1999;8:S107-71.	Subjects aged 20 to 60.	Cases : First mention of multiple sclerosis or central demyelination disorders Controls : For each case were selected up 6 controls from the study matched on age, gender and practice.	HB vaccination before the index date, distributed as recent (date of prescription within 12 months before the index rate) or past (more than one year before).	Conclusions: No “strong” association. Small increase in risk not statistically significant

Touzé E *et al*. *First central nervous system demyelination and hepatitis B vaccination : A pilot case control study* Rev Neurol 2000; 156 (3): 242 – 246.	All patients, which were hospitalized between 1.1.1994 and 31.12.1995 by the Fédération de Neurologie (Salpêtrière Hospital , Paris).	A first episode of demyelinating disorder was defined as Neuro-symptoms, which required consultation with a physician, showing evidence of an attack on the CNS and compatible with attack on white matter , duration of 24 hours or longer , possibly combined with abnormalities on various complementary tests, absence of other explanation.	Exposition is defined as injection of one or more doses of vaccine against HB . It was considered two periods before exposition : 0 –60 and 61 – 180 days.	Conclusions: Data did not permit to exclude an association between HBV and first CNS demyelinating episode

Case-Cross-over

Study and Reference	Methods	Participants	Case	Exposure	Notes
Confavreux, C. *et al* . *Vaccinations and the risk of relapse in multiple sclerosis. Vaccines in Multiple Sclerosis Study Group.* N Engl J Med 2001;344(5): 319-26.	Comparison of exposure to HB vaccine in the 2 months-period preceding relapse with that in control period not followed by relapse.	Patients with diagnosis of probable or definite MS.	Patients included in the European Database for MS who had a relapse between 1993 and 1997 preceded by a relapse-free period of at least 12 months.	HB vaccination (medical records)	Conclusions: HBV does not increase the short term risk of MS relapse.

Cohorts

Study and Reference	Participants	Intervention	Safety Outcomes	Notes
Zipp F *et al*. *No increase in demyelinating diseases after hepatitis B vaccination* Nature Medicine 1999; 5(9): 964 – 965.	134.698 individuals enrolled in a US healthcare database from 1988 to 1995.	HB vaccination	Demyelinating episodes included optic neuritis, myelitis and optic neuritis, demyelinating diseases of the central nervous system, acute disseminated encephalomyelitis and multiple sclerosis.	Conclusions: No difference between vaccinated and unvaccinated at any time

Ecological studies

Study and Reference	Methods	Participants	Intervention	Safety Outcomes	Notes
Fourrier, A.. *Hepatitis B vaccine and first episodes of central nervous system demyelinating disorders : a comparison between reported and expected number of cases*. Br J Clin Pharmacol 2001; 51: 489-490.	Comparison of the expected and reported cases of CNS demyelinating disorders after HB vaccination.	Adults aged between 20 and 44 years, which received HB vaccine between 1.1.94 and 31.12.96.	HB vaccination	First CDD episode within 2 months after a HB vaccine injection.	Conclusion: The possibility of an association between HBV and DD first episode cannot be ruled out.
Sadovnick, D. *et al*. *School – based hepatitis B vaccination programme and adolescent multiple sclerosis.* The Lancet, 2000; 355:549 – 550.	Comparison between vaccinated and non-vaccinated .	Grade – six – students, aged 11-12.	Since October 1992 in British Columbia HBV was offered annually to grade-six-students. From October 92 to September '98 267.412 grade-six-students completed the vaccination series (participation average 92,3,data from the BC Centre for diseases control). In the years preceding the vaccination (from January '86 to September '92) about 41.237 attended grade six annually. Date about the onset of multiple sclerosis were obtained from medical records of the BC Children's Hospital.	Multiple sclerosis onset. There were 9 cases during prevaccination period on 288657, which attended the grade 6 . There were 5 cases out of a total of 289651 grade six students, of whom 267412 (92.3%) completed the vaccination.	Conclusion: No evidence of a link between HB vaccination and DD was found.

Shaw, F.E. *et al*. *Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination.* American Journal of Epidemiology 1988;127(2):337-352.	Comparison of the incidence rate for neurological diseases before and after the introduction o the plasma-derived vaccine. Appropriateness of selection criteria : + Comparability of exposure : -	People that received recombinant HBV at the time of his introduction in the USA (1982, estimated data)	Report of diseases were received from the CDC and FDA. The size of the vaccinated population was estimated through the use of manufacturer's figures (1.6.82. – 31.5.85). For the incidence in the unvaccinated population were used data published since 1959 in US adult population.	Convulsion (5), Bell's palsy (10), Guillan-Barré syndrome (9), lumbar radiculopathy (5), brachial plexus neuropathy (3), optic neuritis (5), transverse myelitis (4).	Conclusion: No conclusive association Between HBV and any neurological consequence.
Subeyrand, B. *Pathologies démyélinisantes du système nerveux central rapportées après vaccination hépatite B par GenHevac B.* La Presse Médicale 2000 ; 29 : 775 – 780.	Comparison between vaccinated and non-vaccinated	Cases of CNS demyelinating disorders reported after receipt of recombinant HBV from May 1989 through December 1998.	Using data on the number of vaccine doses distributed, the authors estimate the number of vaccinated individuals between 1989 and 1998.	Spontaneous report of CNS demyelinating diseases were reviewed. RR was calculated on the basis of the annual average MS incidence of 2/100.000 individuals.	Conclusion: No casual association between HBV and CNS DD

Quality of included studies

Methodological weaknesses of included studies is summarized in Table 2. One study was classified as at low risk of bias (7). No study was classified as at very high risk of bias. The most common methodological weaknesses were lack of validation of cases and lack of specification of vaccine type, dose or content.

Table 2 Summary methodological assessment and risk of bias of included studies.

References & study design	Methodological weaknesses	Risk of bias
Fourrier *et al*. (1) - Case Control	Possible selection bias of cases, date of first symptoms, types of HB vaccines not mentioned, multiple vaccinations unaccounted for in analysis	High
Touzè *et al*. (2) - Case Control	Possible selection bias of cases and controls (taken from neurological hospital), recall bias of exposure	Medium
DeStefano *et al*. (3) - Case Control	Possible attrition bias of controls, recall bias of exposure and date of first symptoms outside HMO	Medium
Sturkenboom *et al*. (4) - Case Control	Possible selection bias (gender) of participants, lack of description of vaccines, dubious generalisability to general population of vaccinated individuals	Medium
Ascherio *et al*. (5) - Case Control	Dubious generalisability to general population from nurses' cohort, likely recall bias as to first onset of symptoms and likelihood of vaccination, unclear and contradictory text, no blinded assessment of exposure mentioned, type of vaccine not mentioned, concurrent vaccines not mentioned.	High
Hernan *et al*. (6) - Case Control	Dubious generalisability to general population of vaccinated individuals, small numerator (11 cases), possible selection bias of cases, no data on number of doses.	High
Payne *et al*. (7) - Case control	Lack of independent medical records review.	Low
Confavreux *et al*. (8) - Case Cross Over	Unclear and contradictory text, vaccines not specified, multiple vaccination not accounted for	Medium
Zipp *et al*. (9) - Retrospective Cohort	Likely selection bias of exposed and unexposed cohorts, ascertainment bias, unspecified HB vaccine exposure, unknown play of concomitant vaccines, 3 year follow-up window from first symptoms unlikely to be sufficient for 100% identification.	High
Fourrier *et al*. (10) - Ecological	Observed/expected incidence model based on assumptions of sales figures of vaccines. Unvalidated cases. Possible selection bias of cases	High
Sadovnick *et al*. (11) - Ecological	Unspecified HB exposure, longer follow-up time for unvaccinated probably introducing bias as the vaccinated were less likely to develop MS in the given time	Medium
Shaw *et al*. (12) - Ecological	Observed/expected incidence model based on assumptions of sales figures of PDV. Unverified cases.	High
Soubeyrand *et al*. (13) - Ecological	Observed/expected incidence model based on assumptions of sales figures of PDV. Unverified cases. Possible selection bias of cases	High

Analysis

Table 3 shows the evidence summary by study design. Because of diversity in study design, case definitions, populations and follow-up times a limited meta-analysis was only possible within our small population of case-control studies. Due to scarcity of data the only meaningful subanalysis was by length of exposure and outcome diagnosis.

Table 3 Single or pooled analysis of data from comparative studies assessing an association between exposure to hepatitis B vaccine, multiple sclerosis and/or demyelinating disease. MS = Multiple Sclerosis; DD = Demyelinating Disease; ON = Optic Neuritis; TM = Transverse Myelitis; RE = random effects model. (a) Odds Ratios were used for case control and case cross over studies, rate ratio was used for ecological studies. (b) In case-control and case cross-over studies the number of MS and/or DD is reported. In cohort and ecological studies person-time denominators are reported. (c) MS probable or definite. (d) MS & Demyelinating Disease. (e) ON + Myelitis & ON + DD of the Central Nervous System + Acute Disseminated Encephalomyelitis + MS. (f) MS + ON + Myelitis. Fixed effects models were used to calculate odds ratios in case-control studies unless otherwise specified.

Multiple Sclerosis and Demyelinating Disease									
Study Design	Case Definition	Time from Vaccination	Number of Studies	Reference to Studies	Pooled Odds Ratio or Rate Ratio (a)	95% Confidence Interval		Overall (b) Population Size	I^2
						Lower Limit	Upper Limit		
Case Control	DD,MS,ON	0-2 months	2	(1,2)	1.63	0.82	3.23	748	0%
	DD,MS,ON	2-12 months	2	(1,2)	1.04	0.66	1.65	798	0%
	DD,MS,ON	0-12 months	5	(1-4,7)	1.18	0.88	1.59	5124	0%
	DD,MS,ON	0-24 months	6	(1-5,7)	1.11	0.84	1.47	5373	0%
	DD,MS,ON	Any time	3	(3-5)	1.04	0.79	1.37	4582	22.3%
	MS(c)	0-12 months	2	(1,6)	1.76	0.86	3.61	2227	0%
	MS(c)	0-24 months	3	(1,5,6)	1.34	0.82	2.19	2491	59.6%
					(RE) 1.46	0.76	3.16		
	MS(c)	Any time	4	(3-6)	1.07	0.80	1.42	5189	71.3%
					(RE) 1.21	0.71	2.08		
	ON	0-6 months	1	(7)	1.49	0.66	3.38	155	n.a.
	ON	Any time	1	(3)	1.22	0.50	3.01	336	n.a.
Case Cross-Over	MS Relapse	2 months	1	(8)	0.66	0.19	2.37	643	n.a.
Cohort	MS, DD (e)	6 months	1	(9)	1.30	0.40	4.80	63,227	n.a.
	MS, DD (e)	1 year	1	(9)	1.00	0.30	3.00	113,221	n.a.
	MS, DD (e)	2 years	1	(9)	1.00	0.40	2.40	162,872	n.a.
	MS, DD (e)	3 years	1	(9)	0.90	0.40	2.10	185,485	n.a.
Ecological	MS	2 months	1	(10)	1.05	0.80	1.37	7,180,000	n.a.
	ON	3 months	1	(12)	0.41	0.08	2.11	136,111	n.a.
	TM	3 months	1	(12)	0.63	0.05	7.60	133,333	n.a.
	MS	Any time	1	(11)	0.55	0.19	1.65	289,651	n.a.
	MS, DD (f)	Any time	1	(13)	0.87	0.71	1.05	10,790,000	n.a.

Whether derived from a meta-analysis or from single studies, the odds ratios or rate ratios within 95% confidence intervals are all non-significant. However recalculation of statistical power of single studies shows that no study had the power to detect a OR smaller than 3.0 at the 5% level significance (a24, a 25).

Some pooled estimates seem to suggest an increased but non-significant risk of MS or DD up to 12 months after vaccination (Figure 2).

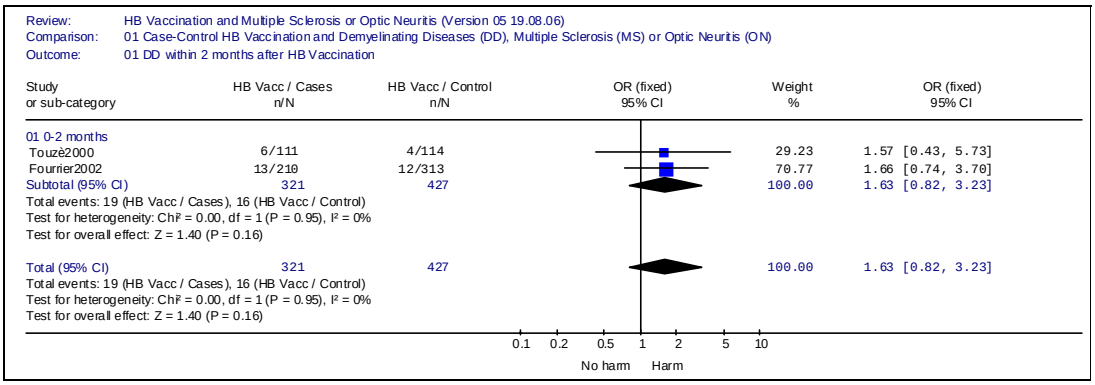

Figure 2 Demyelinating disease (DD) within 2 months of vaccination against HB.

The effect does not appear if the follow-up time is lengthened to 12 months (Figure 3).

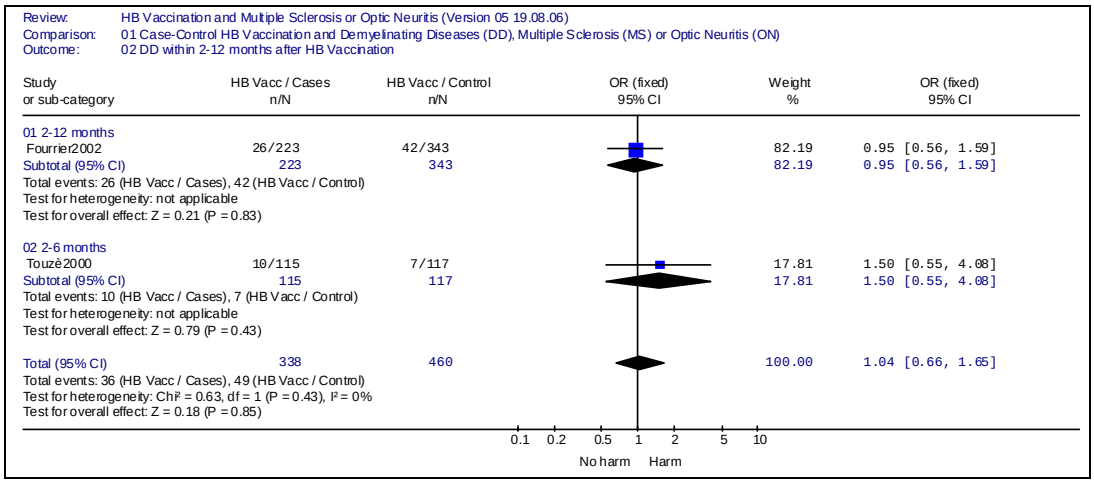

Figure 3 Demyelinating disease (DD) within 12 months of vaccination against HB.

Increasing the size of the data set to over 6000 observations or extending follow up either to two years or open-ended does not significantly affect our estimates (Figures 4, 5 and 6).

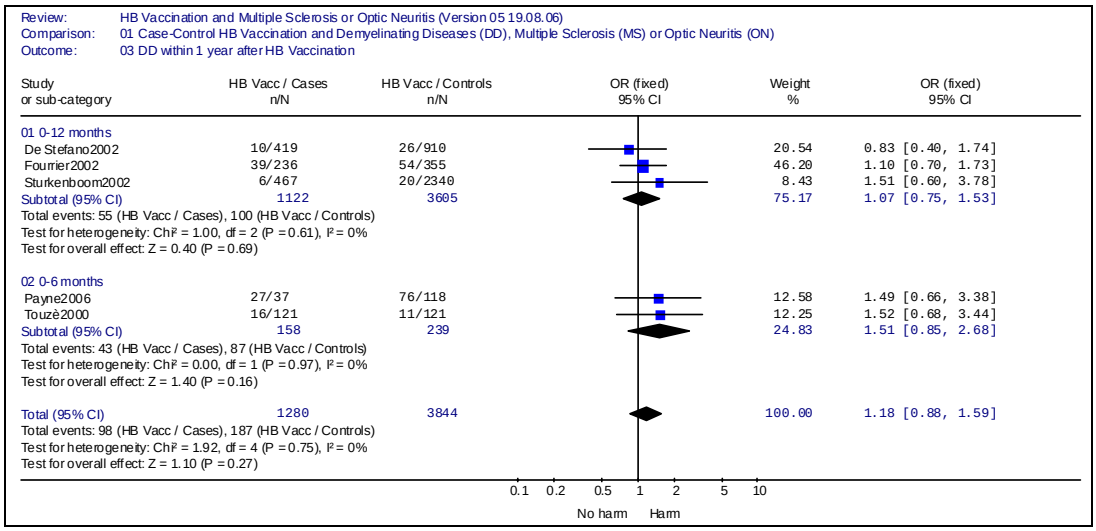

Figure 4 Demyelinating disease (DD) within 12 months of vaccination against HB with a larger dataset.

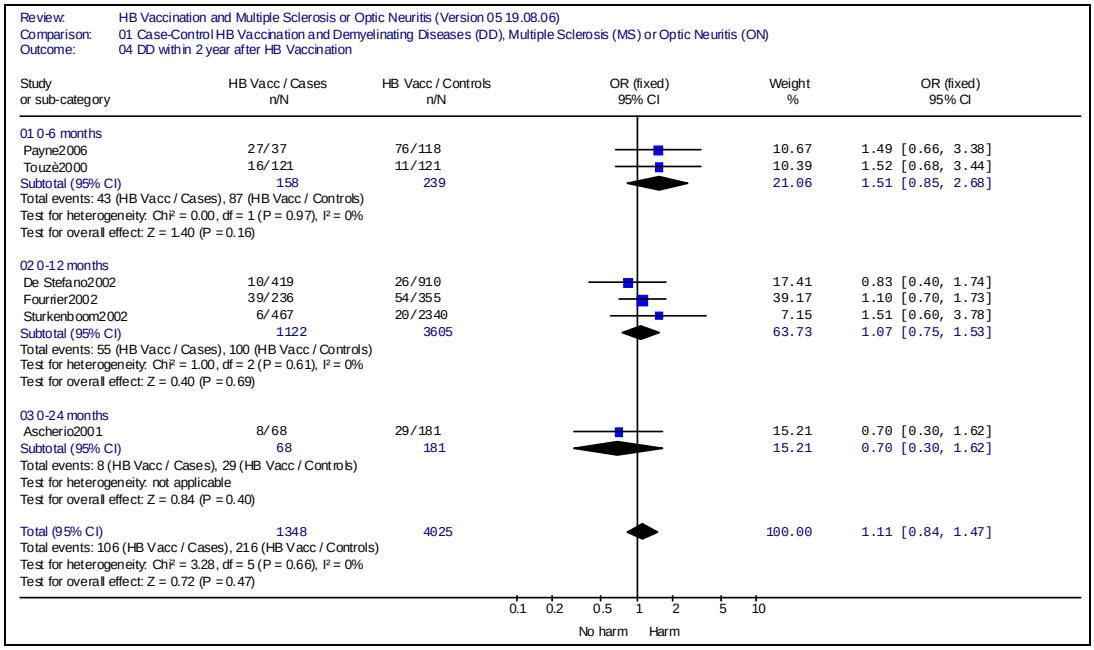

Figure 5 Demyelinating disease (DD) within 2 years of vaccination against HB.

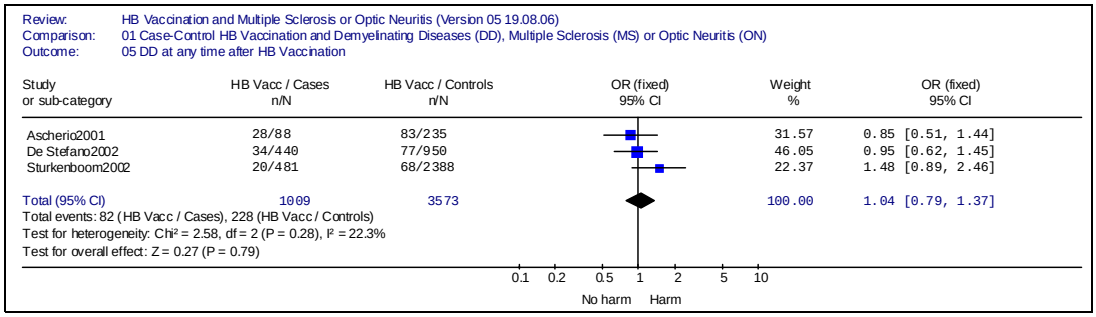

Figure 6 Demyelinating disease (DD) after vaccination against HB.

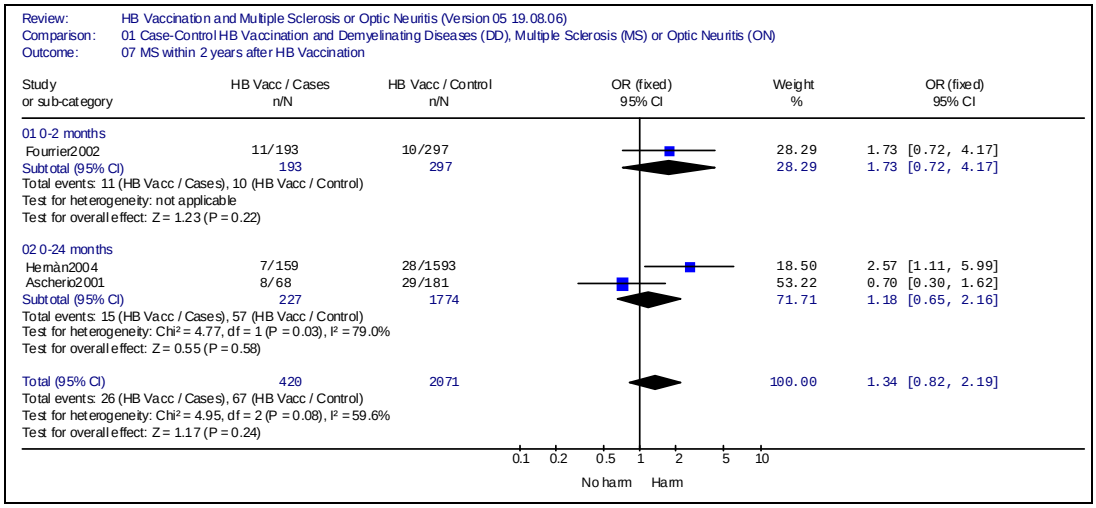

Figure 7 Multiple sclerosis (MS) within 2 years of vaccination against HB.

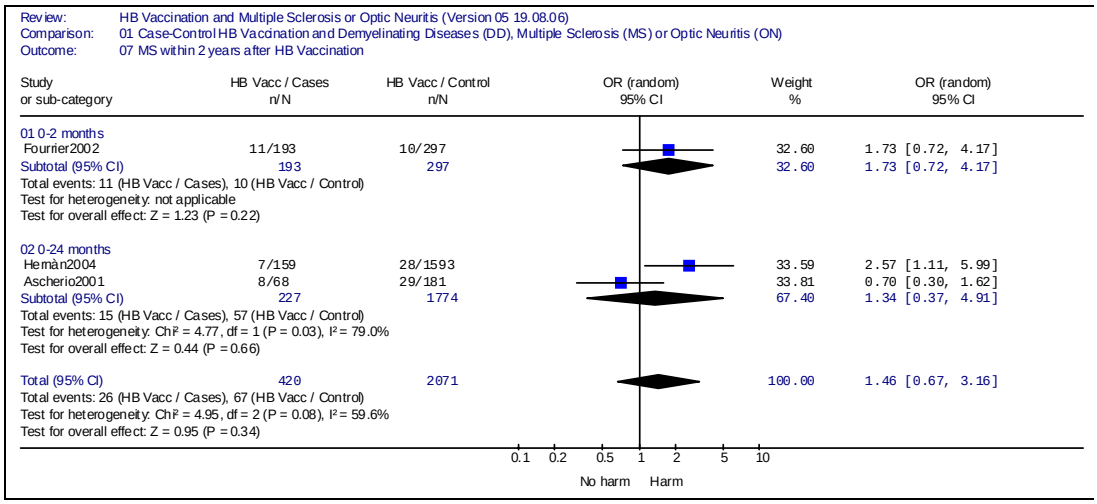

Figure 7a Multiple sclerosis (MS) within 2 years of vaccination against HB (Random effects model).

Meta-analysis of available data including the outlying study by Hernan *et al*. still yields non-significant estimates but introduces considerable heterogeneity (I^2 = 58.3%) into the data set (Figures 7, 7a, 8 and 8a). Possible causes of the observed between-study hetereogenity may be chance, a real variability in the association

and a real otherwise unexplicable heterogeneity between studies. Given the small numbers of studies in the comparison, no conclusions can be drawn.

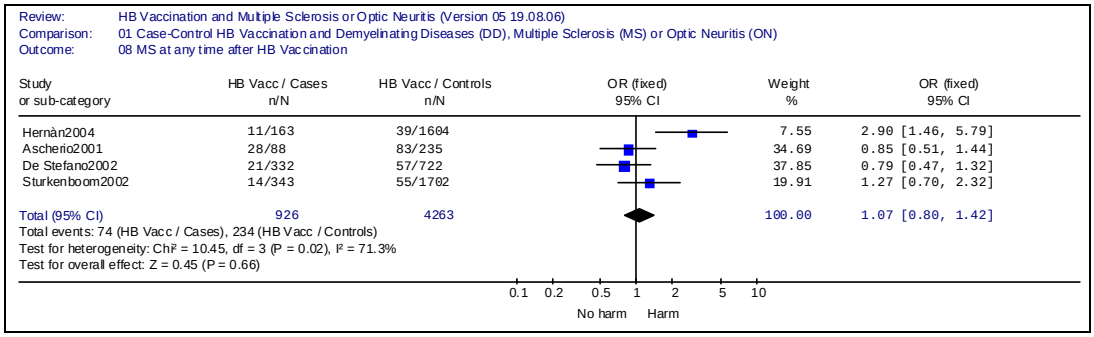

Figure 8 Multiple sclerosis (MS) after vaccination against HB.

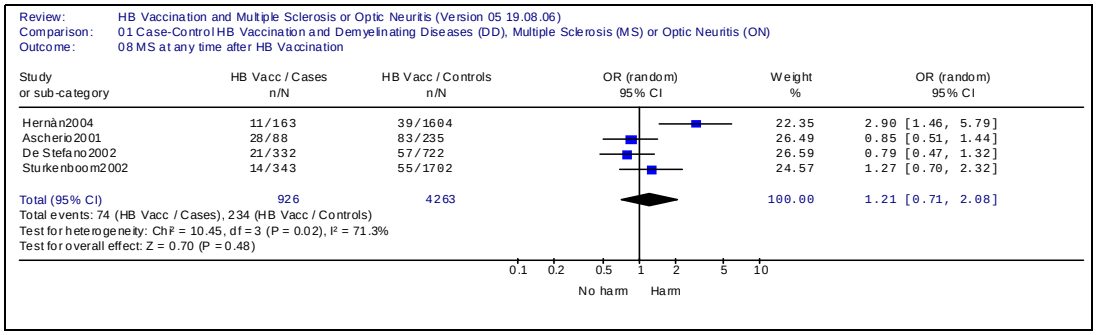

Figure 8a Multiple sclerosis (MS) after vaccination against HB (Random effects model).

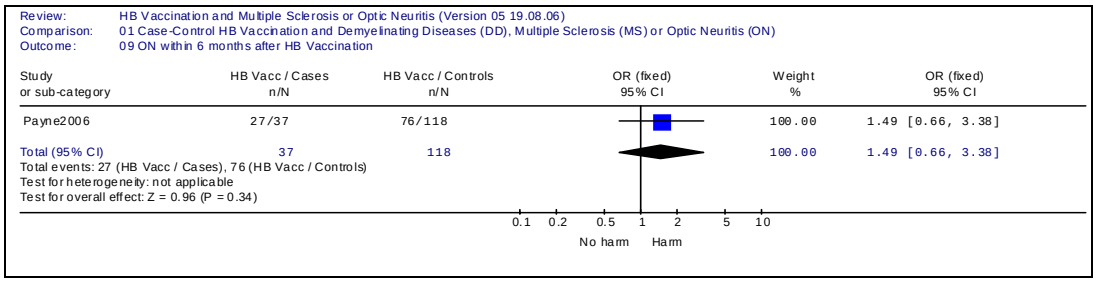

Figure 9 Optic neuritis (ON) within 6 months of vaccination against HB.

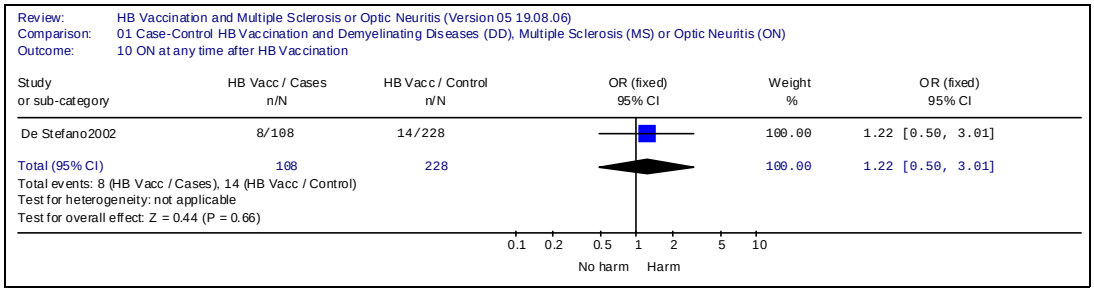

Figure 10 Optic neuritis (ON) after vaccination against HB.

Based on two better quality small datasets (491 observations) there is no evidence that vaccination against HB causes Optic Neuritis (ON).

Despite heterogeneity of diagnostic criteria, further analysis by criteria failed to change our findings. Only three studies defined diagnostic criteria used (Table 4).

Table 4 Case definition criteria used in the three studies reporting them.

Study	Design	Case selection	Criteria used
Ascherio 2001	Nested case-control	MS	Poser CM, Party DW, Scheinberg *et al*. New diagnostic criteria for multiple sclerosis guideline for research protocol. Ann Neurol. 1983;13 227-31.
Hernàn 2004	Nested case-control	MS	Poser CM. The epidemiology of multiple sclerosis: a general overview. Ann. Neurol 1994; 36 (S2): S180-193
De Stefano 2003	Case-control	ON	McDonald WI, Compston A, Edan G, *et al*. Reccomanded diagnostic criteria for multiple sclerosis: guideline from the international pannel on diagnosis of multiple sclerosis. Ann.Neurol. 2001; 50:121-127 Poser CM, Party DW, Scheinberg *et al*. New diagnostic criteria for multiple sclerosis guideline for research protocol. Ann Neurol. 1983;13 227-31.
		MS	Poser CM. The epidemiology of multiple sclerosis: a general overview. Ann. Neurol 1994; 36 (S2): S180-193

Discussion

We have assembled, evaluated and summarized a low quality dataset of retrospective comparative non-randomised studies. Their design varied from case-control, relatively small studies specifically designed to test a hypothesis to very large and powerful ecological studies. These relate population exposure to HB vaccines with the incidence of the demyelinating syndromes. Their power however, is no protection against the play of confounders that can never be discounted in these studies. The data consistently show lack of a significant association between exposure to HB vaccines and onset of demyelinating syndromes. Despite such a finding, the possibility of an association cannot be discounted, especially within the first months following vaccination. In addition, the formulation of a plausible causal hypothesis lends some weight to the possibility of an association.

We were hampered in our task of summarizing evidence by the array of different study designs, definitions, length of follow up and vagueness of reporting of the included studies. It is difficult to formulate recommendations for designing studies capable of adding useful information to our dataset. The gold standard design for assessing a causal association is the randomized controlled trial. However, most currently registered vaccines have been introduced with an evidence base of randomized controlled trials (even within a meta-analysis) insufficient to detect possible rare harms such as MS, especially if occurring months or years after exposure. Considerations of possible harms, especially unknown ones at the time of protocol design, play a small or no part in clinical trials. The increasing number of single or combinations vaccines introduced into paediatric and adult schedules adds to the difficulty of identifying meaningful associations, given that the unexposed windows of controls are reduced or non-existent. Data from the few available or possible placebo-controlled trials are not retained and available to researchers. In this situation retrospective non-randomised “post hoc” (i.e. after the allegation of an association has been made) studies are the only comparative designs possible. A reflection of this methodological straightjacket is the creation and use of designs such as case-crossover in which participants in the study act as their own controls either before exposure to the vaccine or during control periods i.e. periods which the casual hypothesis indicates as at least risk of developing the outcome in question.

In non randomised designs, the possibility of unknown biases coupled with usually poor quality data hinders interpretation of their results and as in the case of

HB vaccines and MS precludes probabilistic conclusions of an association being drawn.

Regardless of the issues, the assessment of the performance of a vaccine cannot be divorced from its objectives, primarily its capacity to prevent disease.

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Conflicts of interest

None.

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44 Zingg W. Does vaccination cause disease?: MACHEN IMPFUNGEN KRANK? Ther. Umsch. 2005; 62(10):665-74. Reason for exclusion: comment.

Appendix A – included study designs

(based on: Farrington 2004, a14; Jefferson 1999, a21; Last 2001, a22)

A *case-control study* is an epidemiological study usually used to investigate the causes of disease. Study participants who have experienced an adverse outcome or disease are compared with participants who have not. Any differences in the presence or absence of hypothesised risk factors are noted.

A *cohort study* is an epidemiological study where groups of individuals are identified who vary in their exposure to an intervention or hazard and are followed to assess outcomes. Association between exposure and outcome are then estimated. Cohort studies are best performed prospectively but can also be undertaken retrospectively if suitable data records are available.

A *time-series* is a comparative design with controls in which measurements are made at different times to allow trend detection and before-and-after exposure assessment.

Case-only design studies

An *ecological study* is a study in which the units of analysis are populations or groups of people rather than individuals. Inference is then made by observing the difference in incidence between populations and the event in question.

A *case-crossover study* is a design in which exposures of individuals during one period is compared by matched-pair analyses to their own exposure during a preceding period of similar length.

Case-coverage design is a study comparing prevalence of exposure in individuals with exposure in the reference population. No denominator data are required and the population coverage information is derived from summary statistics. When coverage information is derived from a population sample, the design is that of a case-base study.

A *self-controlled case series* uses individuals as their own controls. The ages at vaccination are regarded as fixed and the age at the time of an adverse event is the random variable of interest within a pre-determined observation period.

Appendix B – Methodological quality assessment scales

(based on: Wells, a14; Farrington 2004, a15 ; Khan 2000, a23)

Quality item	NEWCASTLE - OTTAWA Scale for Case-Control studies
Selection	1) **Is the case definition adequate?** yes, with independent validation yes, eg record linkage or based on self reports no description
	2) **Representative ness of the cases** consecutive or obviously representative series of cases potential for selection biases or not stated
	3) **Selection of Controls** community controls hospital controls no description
	4) **Definition of Controls** no history of disease (endpoint) no description of source
Comparability	1) **Comparability of cases and controls on the basis of the design or analysis** study controls for _____(Select the most important factor) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)
Exposure	1) **Ascertainment of exposure** secure record (eg surgical records) structured interview where blind to case/control status interview not blinded to case/control status written self report or medical record only no description
	2) **Same method of ascertainment for cases and controls** yes no
	3) **Non-Response rate** same rate for both groups non respondents described rate different and no designation

Quality item	NEWCASTLE - OTTAWA Scale for Cohort studies
Selection	1) **Representativeness of the exposed cohort** truly representative of the average _____(describe) in the community somewhat representative of the average ____ in the community selected group of users eg nurses, volunteers no description of the derivation of the cohort
	2) **Selection of the non exposed cohort** drawn from the same community as the exposed cohort drawn from a different source no description of the derivation of the non exposed cohort

	3) **Ascertainment of exposure** secure record (eg surgical records) structured interview written self report no description
	4) **Demonstration that outcome of interest was not present at start of study** yes no
Comparability	1) **Comparability of cohorts on the basis of the design or analysis** study controls for _____ (select the most important factor) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)
Outcome	1) **Assessment of outcome** independent blind assessment record linkage self report no description
	2) **Was follow-up long enough for outcomes to occur** yes (select an adequate follow up period for outcome of interest) no
	3) **Adequacy of follow up of cohorts** complete follow up - all subjects accounted for subjects lost to follow up unlikely to introduce bias - small number lost >__ % (select an adequate %) follow up, or description provided of those lost) follow up rate < __% (select an adequate %) and no description of those lost no statement

Quality Item	Quality Assessment Scale for Interrupted time-series and Case Cross-Over studies
Were the eligibility criteria specified?	**Adequate**: criteria appropriate to outcomes being measured. **Inadequate**: exclusion criteria impact on outcomes being measured. **Unknown**: no mention in text.
Were objective measurements taken both before and after the intervention?	**Adequate**: relevant data recorded before and after a verifiable intervention. **Inadequate**: non-verifiable intervention points or incomplete data before/after records.
Was the time frame appropriate?	**Adequate**: the outcomes being measured are detectable within the study time frame. **Inadequate**: brevity of time frame precludes accurate measure, e.g. of long-term outcomes. **Unknown**: no mention in text.
Was exposure adequate and appropriate?	**Adequate**: sufficient time to allow plausible association was allowed. Exposure was to the vaccine and no obvious confounding interventions were present.

Quality Item	Quality Assessment Scale for case-only studies
Were the cases selection criteria appropriate?	**Appropriate** – anything likely to minimise the play of confounders e.g., same age and ethnic group
Were the cases comparable for exposure?	**Comparable** -anything likely to minimise the play of confounders e.g., same type of records.
Were the outcomes verifiable?	**Verifiable** – anything likely to minimise the play of confounders e.g., all made with MRI scan.
Were the conclusions of the study justified by the evidence presented?	**Justified** – anything likely to minimise the play of confounders e.g., stock taken of the limitations of the study and alternative explanation offered.