The future of the National Immunisation Programme: towards a programme for all age groups
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Dear minister,

I am pleased to enclose the advisory report ‘The future of the National Immunisation Programme: towards a programme for all age groups’, which has been reviewed by the Standing Committees on Infection & Immunity, Medicine, and Ethics & Law.

The report contains an analysis of the programme’s effectiveness to date and identifies scientific developments in the fields of immunology, vaccinology and communication science, which may be relevant to the future of the programme. In addition, an assessment framework is put forward, which includes a set of criteria for the inclusion of a vaccination in a public programme. No such framework – which may be likened to Wilson and Jungner’s screening criteria – has hitherto been available, at either the national or international levels. The framework was recently presented to the Federation of European Academies of Medicine, where it was well received.

The committee responsible for the report makes the point that health care practitioners require considerable knowledge and skill in order to discuss vaccination issues with parents and to provide them with the information they need. I fully endorse the committee’s conclusion that it is therefore very important that medical training courses pay adequate attention to vaccinology and to discussion and communication skills. These subjects should be systematically addressed by the basic and refresher training given to nurses, doctors, youth health care practitioners, GPs, paediatricians and internists. Finally, I would draw your particular attention to the committee’s recommendations regarding the monitoring of and research into parents’ willingness to have their children vaccinated.

Yours sincerely,

(signed)

Professor JA Knottnerus
The future of the National Immunisation Programme: towards a programme for all age groups

to:

the Minister of Health, Welfare and Sport

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The future of the National Immunisation Programme: towards a programme for all age groups
Executive summary

An appropriate moment to consider the future of the NIP

Since 1957, Dutch children have been vaccinated against infectious disease through the National Immunisation Programme (NIP), usually at clinics for infants and toddlers. The programme prevents a great deal of disease and death. Initially, vaccination was provided against diphtheria, whooping cough, tetanus and polio. Later, the programme was extended to also provide protection against measles, German measles, mumps, hepatitis B, and infection by Haemophilus influenzae type b, meningococcus C and pneumococci.

Since 2005, management of the programme has been the responsibility of the Centre for Infectious Disease Control (Dutch initials: CIb), part of the National Institute of Public Health and the Environment (RIVM). The Netherlands Vaccine Institute (NVI) produces or sources the vaccines used for the Programme. Finally, the Health Council plays an advisory role in relation to all these activities. The Council identifies and assesses scientific information about vaccination and makes appropriate recommendations regarding the scope and content of the NIP.

The programme’s fiftieth anniversary provides an appropriate opportunity to review the range of vaccinations provided, and to consider the NIP’s future. After all, neither science in general nor epidemiology in particular stands still. In recent years, for example, various new vaccines have become available, raising a number of important questions.
Is it desirable to continue providing all the vaccinations currently included in the programme? What additional vaccinations should be considered for future inclusion? To answer these questions, it is helpful to begin by considering the past: what has the programme achieved to date? It is also desirable to have an assessment framework: what are the grounds for inclusion in the NIP? A clear set of criteria is required. Once defined, such criteria can be used to arrive at transparent rational decisions regarding and priorities for the future of the NIP.

**NIP prevents a great deal of disease and death**

The NIP makes a very considerable contribution to the prevention of death and disease among children. The introduction of universal vaccination has virtually eliminated death from polio, diphtheria and infection by *Haemophilus influenzae* type b and meningococcus C. The recently introduced vaccination against pneumococci is also expected to have a considerable effect on mortality.

The programme’s impact on the disease burden is also clear. Since the introduction of universal vaccination, polio epidemics have been rare and confined to non-vaccinated pietistic reformed Christian communities. Diphtheria and tetanus are all but eradicated from the Netherlands, and measles is now very unusual. The number of hospital admissions due to congenital rubella syndrome has fallen from forty in 1980 to less than one a year since 1987. Vaccination against mumps, also introduced in 1987, has also been very successful. Prior to the provision of mumps vaccine through the programme, between three hundred and eight hundred children were being admitted to hospital with mumps-related meningitis each year. Today, such cases occur only sporadically.

Following the introduction of vaccination against *Haemophilus influenzae* type b in 1993, invasive infections fell sharply, from around seven hundred a year to twelve in 1999. Since then, however, the number has edged back up again, to forty-nine in 2004, possibly because of a decline in the number of natural re-infections. In other words, the Hib vaccination is effective, but further research is required into its long-term protective effect and interaction with other vaccinations.

The addition to the programme of vaccination against meningococcus C, in 2002, has similarly led to a marked decline in invasive infections. Although the impact of the newly introduced vaccination against pneumococci is not yet known, it is expected to have major benefits both for the children who receive it and, indirectly, for adults.

Vaccination against hepatitis B is now successfully provided to two population groups through the NIP: children whose mothers carry the virus and children
with at least one parent from a country where hepatitis B is prevalent. In both cases, the result has been the alleviation of the considerable disease burden associated with chronic infection and the existence of carriers within the population.

Where whooping cough is concerned, the situation is more complex, although here again a great deal of illness and also deaths have been avoided by vaccination. After a prolonged period in which the vaccination was very effective, its effectiveness has been declining since the 1990s. As a result, there have been occasional whooping cough epidemics in the Netherlands. In response, a new acellular whooping cough vaccine was introduced in 2005. A problem is that the protection afforded by vaccination against whooping cough lasts only six to eight years. It is unclear what additional measures should be taken to protect very young infants who have yet to begin or complete the vaccination programme. Such infants form an important population group in this context, since they are more vulnerable than other age groups if they contract the illness.

Adverse reactions relatively uncommon

The Netherlands has what is known as a passive system for the registration of adverse reactions to vaccination through the NIP. From the data collected, it is apparent that the vaccinations provided rarely, if ever, trigger serious adverse reactions (i.e. death, serious neurological phenomena or permanent physical injury). The data on less serious transient adverse reactions are less reliable, since such reactions often go unreported.

Since 2004, active focused efforts have been made to determine the frequency of adverse reactions. The proper study of such reactions is particularly important for the acquisition of reliable data concerning the less serious transient phenomena associated with vaccination. It is also valuable as a means of assessing the level of reporting through the established registration system and answering specific questions, such as the effect of changing a particular vaccine.

A high vaccination rate remains important

At present, the vaccination rate achieved by the NIP is more than 95 per cent. However, there are clear geographical differences. For example, in parts of the country with high concentrations of pietistic reformed Christians, some of whom have conscientious objections to vaccination, the vaccination rate is well below the national average.

Such clusters of non-vaccinated people have become very important in relation to the epidemiology of polio, measles and German measles in the Nether-
lands. The reason being that where the vaccination rate is below 90 to 95 per cent, epidemics are possible. Since 1990 there have been epidemics of polio (1993), measles (1999-2000) and German measles (2004-2005) in parts of the Netherlands with significant pietistic reformed Christian populations.

It is not unreasonable to fear that further such epidemics might occur in the future. Such epidemics could lead to infection spreading to other population groups that are not well protected. There is also a risk that contact between Dutch pietistic reformed Christians and similar communities in other countries could result in the reintroduction of a micro-organism that has been eliminated from the Netherlands. In the past, such contacts have certainly resulted in the communication of polio, measles and German measles from the Netherlands to communities in other countries following localised outbreaks here.

**New target groups require consideration**

The NIP was originally set up to combat childhood illnesses. With good reason, the programme continues to focus primarily on the vaccination of children. However, the developments surrounding whooping cough have illustrated that older children and adults can also play a key role in the spread of pathogens. It is therefore pertinent to ask whether and, if so, to what extent the vaccination of older children and adults is desirable as well.

Consideration should additionally be given to the question of what constitutes an appropriate period of protection. May a vaccinated individual reasonably expect lifelong protection? In practice, the period of protection is often shorter, but under the present circumstances the risk to adults is too small to justify universal revaccination. In the future, however, that situation may change.

Another shift in emphasis evident within the programme has been the increasing focus on older people. Influenza vaccination is already provided for older people, and it is likely that there will soon be a vaccine suitable for protecting this population group against shingles.

In the future, the availability of vaccines against sexually transmissible diseases may warrant the immunisation of other population groups as well. Such vaccines are best given at the age of eleven or twelve. A vaccine against human papilloma virus, which plays an important role in the development of cervical cancer, is already available.

The extent of the realignments and their implications for selection of the NIP’s target groups are not entirely clear. However, it seems probable that the NIP will increasingly become a programme for all age groups.
**Greater understanding of the immune system opens the way for additional vaccines**

In the past, use was made of vaccines that had been found to work in practice, without it necessarily being clear how they worked. Nowadays, a lot more is known about the immune system, and this knowledge can be used in the development of vaccines. Developers can now draw on DNA techniques (*genomics*) and protein chemical techniques (*proteomics*). Information technology is also important in the search for antigens that could form the basis for new vaccines. Furthermore, certain interesting discoveries have recently been made regarding the way the innate immune system works.

Nevertheless, in many instances not enough is known about the immune system to support vaccine development. It has not so far been possible, for example, to create vaccines against diseases that under natural circumstances do not lead to the acquisition of effective immunity. Medical science is presently able to provide vaccines primarily against diseases that naturally result in the acquisition of long-term immunity.

Increasing scientific knowledge has, however, provided answers to various key questions. There is no convincing evidence that allergic conditions have become more common as a result of vaccination. Indeed, research designed to test the ‘hygiene hypothesis’ has yielded no evidence that the immune system can be compromised by lack of exposure to certain infectious diseases. It is also now known that the immune system is quite capable of coping with very large numbers (thousands) of antigens. There is therefore no reason to suppose that the immune system can be overloaded or otherwise adversely affected by exposure to different antigens, as happens in the NIP. However, it may be that some vaccines are less effective when several are administered together.

**Good public information essential**

In recent years, a great deal of effort has been put into the provision of public information via leaflets, websites and outreach activities. It is of particular importance that the vaccination rate is not allowed to decline.

A decline is a real danger as the illnesses against which protection is provided become less familiar, and the perception that a health risk would exist without vaccination consequently fades. If this in turn were to result in a lower vaccination rate, the programme could become the victim of its own success. Another consideration is that people nowadays obtain information from a variety
of sources and are increasingly inclined to make their own judgements. It is important that information about the NIP is geared to this changing setting. This implies clear communication of the advantages and disadvantages of participation and therefore the availability of well informed and well trained care practitioners.

In this context, it is also important to conduct systematic, regular research into public willingness to submit to vaccination. How receptive are people in different population groups – e.g. well-educated parents – to consent to (their children’s) participation? What factors are influential in this regard? Where new communication strategies are adopted, their effectiveness in use should be monitored.

New assessment framework to support informed decision-making and prioritisation

The protection of the public and society against serious infectious disease by vaccination: this is the NIP’s stated general objective. There are three ways of realising this objective.

The first is the eradication of disease. This is feasible where certain illnesses are concerned (as seen with polio and smallpox), but not in all cases. Where eradication is not possible, the achievement of group or herd immunity is the next option. This involves achieving a level of immunity within a population, such that an infectious disease has very little scope to propagate itself, even to non-immunised individuals. To this end, it is necessary to achieve a high general vaccination rate. If this second strategy is not feasible either, the third option is to protect as many individuals as possible.

Attainment of the programme’s general objective depends on making appropriate decisions about the vaccination of particular target groups. To date, there has been no standard national or international framework for the assessment of vaccination options. This shortcoming has now been corrected by definition of the following seven criteria for the provision of a given form of vaccination for a given group:

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.

2 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 symptoms.
• The necessary vaccination rate is attainable (if eradication 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.

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.

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.

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

Provision of all present vaccinations should be continued

All the vaccinations currently provided through the NIP have been assessed against the seven criteria. All were found to satisfy the criteria and their provision should therefore be continued.

New vaccines should be included in due course

The committee has assessed the merit of providing various age groups with vaccination against each of a variety of conditions in the context of a public vaccination programme. Consideration was thus given to: the vaccination of young children against chicken pox, invasive meningococcus B infection, influenza, respiratory syncytial virus infection, intestinal rotavirus infection, tuberculosis, hepatitis A, smallpox, gastrointestinal ulcers and stomach cancer caused by Helicobacter pylori, hepatitis C, group A haemolytic streptococcus infection and Lyme disease; the vaccination of pre-pubescent children against human papilloma virus infection, herpes simplex type 2 virus infection, cytomegalovirus infection, HIV/AIDS infection, pelvic inflammatory disease caused by Chlamydia trachomatis and gonorrhoea; the vaccination of women who hope to have
children against group B haemolytic streptococcal infection; the vaccination of older people against influenza, shingles and invasive pneumococcal infections. The most appropriate age for universal vaccination against hepatitis B has yet to be ascertained.

In fifteen of the twenty-three cases, the committee concluded that the disease burden was considerable and that provision of the vaccination in a public programme would therefore be desirable. However, in no case – even where a vaccine is already available – is the committee presently prepared to make an unqualified recommendation that vaccination be included in the programme. Where chicken pox, hepatitis B, intestinal rotavirus infection and cancer resulting from human papilloma virus infection are concerned, the committee believes additional analysis is required in the short term in order to determine the importance and urgency of providing vaccination.

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**Research and training can enhance implementation of the programme**

The NIP should meet high standards, not only in terms of its effectiveness and safety, but also in terms of its implementation. To this end, the committee has made a number of recommendations concerning monitoring and effect investigation, concerning research into adverse reactions, public information and communication, concerning the conditions for research projects in the NIP population, and concerning initial and in-service training.
Chapter 1

Introduction

1.1 Ministerial requests for advice

Since 1957, the Netherlands has had a National Immunisation Programme (NIP): a public programme of vaccination against infectious disease. The programme prevents a great deal of disease and death. It is operated by the infant and toddler clinics of the child health care system, because the focus has traditionally been primarily on the vaccination of children. However, since 2005, management of the programme has been the responsibility of the Centre for Infectious Disease Control (Dutch initials: CIb), part of the National Institute of Public Health and the Environment (RIVM). The Netherlands Vaccine Institute (NVI) produces or sources the vaccines used for the Programme.

The Health Council plays an advisory role in relation to all these activities. The Council identifies and assesses scientific information about vaccination and makes appropriate recommendations regarding the scope and organisation of the NIP. Accordingly, when considering changes to the programme, the minister also seeks the Council’s advice.

In this context, the Council regularly provides advice regarding particular vaccinations. However, from time to time, the programme as a whole is reviewed. This report is one such review, being devoted to the future of the National Immunisation Programme. It follows on from an RIVM report entitled *Towards a Dutch National Vaccination Programme for the 21st Century*, which
appeared in September 2000 and provided an analysis of likely relevant developments in the field of vaccines and vaccination between 2000 and 2020. Each of the vaccines then available or expected to become available was assessed and conclusions drawn about its ability to reduce disease burden, its efficiency and its suitability for inclusion within the programme. The report also considered whether it was necessary to make changes to the vaccines then included in the NIP and various measures were recommended with a view to maintaining and improving the programme’s results.

On 29 September 2000, the Minister of VWS asked the Health Council to make an appraisal of the RIVM report. The content of the minister’s letter is reproduced in appendix A. In response to developing situations, the Council has since already reported on vaccination against meningococcus C and pneumococci (January 2002 and October 2005), against hepatitis B (February 2001 and August 2003) and against whooping cough (April 2004).

Now, the Health Council is ready to make its broader report on the future of the NIP. In this report, the committee behind the report has been able to draw upon updates of the RIVM’s original 2000 report that prompted the minister to request this review.

The report begins by outlining the history of the NIP and summarising current scientific knowledge and thinking in the disciplines of immunology and public information. Thereafter, the basis on which the Council has assessed the various forms of vaccination is described. The report goes on to consider the fifteen vaccines currently administered through the NIP and twenty-three ‘candidate’ vaccines; in each case, an assessment is made of the importance of retaining or including the vaccine within the programme. Specifically, this report seeks to address the following questions:

Knowledge
1. How has the NIP developed since 1957?
2. How effective is the programme?
3. What do we know about the way the immune system works?
4. What do we know about the provision of information to target vaccine recipient groups?
Context
5 What are the main objectives of the NIP?
6 What criteria are applied when deciding whether a particular vaccination should be made available to a particular target group?

Options
7 What new forms of vaccination are likely to become possible in the foreseeable future?
8 Which of the existing vaccinations should be retained in the programme, and which other vaccinations should be added to it now or are likely to be desirable in the longer term?
9 How should the revised programme be run?

1.2 The committee and its methodology

In response to the minister’s requests for advice, the President of the Health Council established the National Immunisation Programme Review Committee on 13 June 2001, for a period of five years. The Committee’s members are listed in appendix B.

It is important to specify at the outset how the Committee defines a number of terms that are central to this report. By ‘vaccine’, the Committee means a preparation that helps the immune system to build immunity against disease. Vaccination is the administration or use of one or more vaccines. Most vaccines are administered by subcutaneous or intramuscular injection, but some are administered orally or nasally. Vaccines that protect against infectious disease are derived from or based on (parts of) micro-organisms.

A great deal of experience has been acquired in the use of vaccines to prevent infectious disease. Gradually, however, vaccines designed to protect against non-infectious diseases are also being developed. In principle, it is possible to influence the immunological processes associated with any condition in relation to which the immune system plays a role. Where such influence is exerted with a view to preventing disease, the vaccines involved are referred to as preventive or prophylactic vaccines; where the object is the treatment of an existing condition, the vaccine is described as therapeutic.

The Committee collated relevant scientific information by means of a literature study. Hearings were organised for various parties, including representatives of the pharmaceutical industry, the Netherlands Vaccine Institute and various community organisations. Furthermore, the Committee consulted experts from
the Netherlands and other countries; a list of those consulted is presented in appendix B.

In line with the minister’s request, the Committee confined its deliberations to the use of vaccines in programmes whose purpose is explicitly public, such as the NIP. The existing NIP, which is focused mainly on children, was therefore the starting point for the Committee’s review. However, the NIP is gradually becoming a programme for people of all ages. The Committee's assessment method was therefore designed to be appropriate in relation to all forms of vaccination with a public objective.

Hence, the Committee considered the provision of advice on forms of vaccination intended to benefit people individually to be outside its remit. So, for example, this report does not consider vaccination for travellers, for particular patient groups (such as those with impaired immune function), or for particular professions. Nor is the question of vaccination in response to disease outbreaks considered.

The Committee was asked to report in phases, addressing first the period up to 2010 and subsequently longer-term developments. However, the existing report deals not only with the near future, but also with developments beyond 2010, insofar as anything worthwhile can yet be said about them.

1.3 Structure of this report

This report is in three parts: Knowledge, Context and Options. In section 2 – the first section of Part 1, which sets out relevant knowledge – describes the development of the NIP. Section 3 summarises recent advances in immunology, while section 4 is devoted to knowledge about the communication of public information. Part 2 of the report, which deals with the assessment method used by the Committee, begins with a statement of the NIP’s objectives in section 5. Section 6 then sets out the seven criteria used to decide whether a vaccination should be included in the programme. Part 3, the examination of options for the programme, starts with a schedule of candidate vaccinations (section 7). In section 8, the Committee goes on to consider which old and new vaccinations should be included in the NIP, now or at some future date. Finally, section 9 of the report looks at the question of how the programme should be run.
2 Developments in the Programme
3 Recent advances in immunological science
4 Developments in the field of public information and communication

Knowledge
The future of the National Immunisation Programme: towards a programme for all age groups
Developments in the programme

2.1 The development of the existing programme

How did the NIP come into being and what considerations have previously motivated decisions to include new vaccinations in the programme? Not all the decisions that have shaped development of the NIP, or the reasoning behind them, prove to be well documented. The programme had no formal start and has no statutory basis. A public programme for tackling childhood diseases by vaccination simply evolved in clinical practice, out of a general sense of responsibility, to begin with primarily for the health of children. The medical profession wished not only to protect individual children against infectious disease, but also to achieve high vaccination rates, so that the entire population or large population groups were safe from the diseases in question. To provide insight into the programme’s history, the Health Council asked Vos and Richardus to document the relevant developments.9

2.1.1 Smallpox vaccination: the first public vaccination programme

Since smallpox has not been a characteristic disease of childhood since the late nineteenth century, the introduction of smallpox vaccination cannot be seen as the start of the NIP, whose objective was to address disease in children. Never-
theless, smallpox vaccination was the first form of vaccination to be made available in the context of a public programme.

Vaccination against smallpox has been considered by the Health Council on several occasions. The subject was apparently quite contentious, since the Council’s reports did not all have unanimous support. The key developments in the history of smallpox vaccination are identified below, since they raise questions concerning effectiveness, adverse reactions and compulsion that are relevant to the way public vaccination programmes are organised today.

Key developments

From 1823, a child could not be admitted to primary school without a ‘vaccination certificate’ signed by a vaccinator. Since few people had access to education at that time, it is difficult to interpret this requirement as a sign that a public vaccination programme had been established. The vaccination rate remained very low. This indirect form of compulsion was scrapped in 1857.

Between 1870 and 1872, however, the Netherlands was hit by a major smallpox epidemic: the last on such a scale. In 1871, roughly 16,000 people died of smallpox – 20 per cent of the total number of deaths in that year. In response, the vaccination certificate requirement (and thus indirect compulsion) was reintroduced (Infectious Disease Act, 1872). This created a problem for children whose parents had fundamental objections to vaccination, since they were excluded from education. To exacerbate the situation, the Compulsory Education Act of 1900 made schooling obligatory up to the age of twelve.

The combination of compulsory education and the vaccination certificate requirement led to a sharp rise in the vaccination rate. Implementation of the Compulsory Education Act may therefore be seen as the birth of a public vaccination programme against smallpox in the Netherlands. By that time, public vaccination programmes already existed in various other countries, such as Germany, where vaccination against smallpox had been obligatory since 1834. Until 1900, the control of smallpox in the Netherlands was relatively ineffective compared with neighbouring countries. Between 1893 and 1898, for example, there were 38.7 smallpox deaths per million of the population in the Netherlands, while in Germany there were just 1.1 deaths per million.¹⁰

From 1902, the Anti-Revolutionary Party and the Christian Historical Union repeatedly proposed making the law less strict. However, the Health Council continued to advocate indirect compulsion and ministers continued to accept the Council’s advice. Until 1928, that was, when indirect compulsion was ended.
Developments in the programme 25

after intense debate regarding an association between encephalitis and smallpox vaccination (encephalitis postvaccinalis). Although the Health Council advised maintenance of the status quo, the minister of the day decided to suspend compulsion, initially for one year; in fact, the suspension remained effective until 1939.

By that time, the vaccination rate had fallen to a very low level, giving rise to strong calls for direct compulsion. The argument was that the low vaccination rate had made the Netherlands vulnerable to the introduction of epidemics from abroad.

The situation called for a more structural solution. Because of the constitutional and political issues involved, a state commission chaired by Minister Romme was set up to look into the matter in 1938. This commission decided that the answer was to reduce the age of vaccination. At that time, it was normal in the Netherlands for children to be vaccinated shortly before reaching school age. However, encephalitis postvaccinalis was more common following vaccination at that age than following earlier vaccination. The commission’s recommendation that vaccination should be performed in the first year of life was accordingly incorporated into the 1939 Vaccination Act. This Act did away with indirect compulsion where vaccination itself was concerned, but introduced compulsory appearance: parents could decline to have their children vaccinated, but had to appear before the mayor and explain their reasons.

Before the Second World War, smallpox vaccination was popularly closely associated with access to education in the Netherlands. The 1939 Vaccination Act broke this link and made smallpox control more systematic. In a certain sense, therefore, the smallpox vaccination system became a precursor of the NIP at that point.

Reducing the age for vaccination had the desired effect: a fall in the rate of encephalitis postvaccinalis relative to the number of vaccinations performed. However, encephalitis cases did not decrease in absolute terms. Indeed, as the vaccination rate rose there was initially a rise in the number of cases. The programme consequently remained contentious.

As international smallpox control became more effective, debate concerning the advantages and disadvantages of vaccination intensified. In the postwar period, the Health Council published several further reports on the subject of smallpox vaccination, with notable publications appearing in 1966, 1968 and 1971. In 1975, the government repealed the Vaccination Act, on the Council’s advice. Thus universal vaccination against smallpox came to an end in the Neth-
In 1981, the World Health Organisation (WHO) declared that smallpox had been globally eradicated.

**Important lessons**

Various lessons can be learned from the history of smallpox vaccination. After the last major epidemic in 1870 to 1872, smallpox became an exotic disease in the Netherlands. The current epidemiological thinking is that, under such circumstances, universal vaccination of entire year cohorts of children is not necessary. Therefore, mass vaccination was continued unnecessarily for a longer period. It would have been sufficient to isolate patients and employ ring vaccination (the vaccination of patients’ contacts). In hindsight, indirect compulsion was also unnecessary and may not have been effective. Unnecessarily obliging people to submit to vaccination provided the critics of vaccination with grounds for opposition right up to the 1970s.

Important lessons can also be learnt from the history of *encephalitis postvaccinalis*. Until 1924, the condition was unknown, and exactly why it became prevalent thereafter remains a mystery. What is known is that it was associated with smallpox vaccination. Its incidence varied substantially from country to country and was relatively high in the Netherlands. However, it is by no means certain that this had to do with the vaccine used in the Netherlands, since cases also occurred when vaccines from countries with very low incidences were used. Several dozen children died of the condition in the Netherlands.

Encephalitis was relatively common following the vaccination – especially the primary vaccination – of older children and adults. This meant that the vaccination of military personnel and travellers (who, along with children and medical personnel were among the main target groups for vaccination) was particularly problematic. The solution was found to be the administration of vaccinia immunoglobulin at the time of vaccination.

The iatrogenic encephalitis epidemic could largely have been avoided by ring vaccination.\textsuperscript{11,12} This observation is relevant in the modern context, since in the event of the smallpox virus being used as a bio-weapon, universal vaccination is unlikely to be desirable.\textsuperscript{13} Only if the initial smallpox infections were not picked up sufficiently quickly would mass vaccination (possibly of a defined population) be a necessary adjunct to the policy of ring vaccination.\textsuperscript{14,15}
2.1.2 DTP-polio: the real start of the NIP

In the first half of the twentieth century, vaccines against several major childhood diseases – diphtheria, whooping cough and tetanus – became available. By that time, these vaccines had been developed to the point where they were of a quality suitable for use in public programmes. In the Netherlands, a vaccine against diphtheria, whooping cough and tetanus was made available free of charge from 1953 for mass vaccination by GPs, clinics, school medical services and municipalities. This DTP vaccine was produced by the National Institute of Public Health (RIV).

Then, in 1955, a vaccine against polio was registered in the USA. This was Salk’s injectable polio vaccine (IPV), made from inactivated polio virus. Most countries ultimately chose to tackle polio using another type of vaccine, namely oral polio vaccine (OPV). Consisting of attenuated living polio virus and administered orally, OPV became available in the early 1960s. Nevertheless, an injectable vaccine was attractive because it could be combined with DTP to form a single combination vaccine. This was one of the main reasons why IPV was adopted in the Netherlands.

Following the polio epidemic of 1956, which affected 2,200 people between May and September, the Health Council advised the Minister of Health to give the Medical Inspectorate (GHI) the task of organising a vaccination campaign and to instruct the RIV to start producing IPV. The minister accepted the Council’s recommendations. So it was that, under the supervision of the GHI, vaccination communities were set up within the infant and toddler clinics of the existing child health care system with the aim of providing every child in the Netherlands with protection. The campaign was organised in 1957, in close collaboration with the Association of Dutch Municipalities, Red Cross organisations and municipal health services. This mass vaccination campaign to protect children against polio led to the creation of a national vaccination programme specifically for children. The campaign may therefore be regarded as the real start of the NIP. All children born after 1945 were invited for vaccination.
2.1.3 The present programme

Since 1962, various other forms of vaccination have been added to the NIP, as indicated in table 1. The programme’s present-day vaccination schedule is set out in table 2.

Table 1 Vaccinations introduced to the NIP, 1957-2006.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Year</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria (D)</td>
<td>1957a</td>
<td>Until 1962 in the form of DTP, subsequently in the form of DTP-polio, since 2003 in the form of DTP-polio-Hib-(HepB)</td>
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<tr>
<td>Tetanus (T)</td>
<td>1957b</td>
<td>Until 1962 in the form of DTP, subsequently in the form of DTP-polio, since 2003 in the form of DTP-polio-Hib-(HepB)</td>
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<tr>
<td>Whooping cough (pertussis, P)</td>
<td>1957b</td>
<td>Until 1962 in the form of DTP, subsequently in the form of DTP-polio, since 2003 in the form of DTP-polio-Hib-(HepB)</td>
</tr>
<tr>
<td>Polio</td>
<td>1957b</td>
<td>Until 1962 separately, subsequently in the form of DTP-polio, since 2003 in the form of DTP-polio-Hib-(HepB)</td>
</tr>
<tr>
<td>Rubella (R)</td>
<td>1974</td>
<td>Until 1987 only for eleven-year-old girls, subsequently in the form of MMR for boys and girls</td>
</tr>
<tr>
<td>Measles (M)</td>
<td>1976</td>
<td>Until 1987 separately, subsequently in the form of MMR</td>
</tr>
<tr>
<td>Mumps (M)</td>
<td>1987</td>
<td>In the form of MMR</td>
</tr>
<tr>
<td>Hepatitis B (HepB) - children of carriers</td>
<td>1989</td>
<td>Children of HBsAg-positive mothers (virus carriers); incorporation into NIP formalised in 2003; separately and in the form of DTP-polio-Hib-HepB</td>
</tr>
<tr>
<td>Haemophilus influenzae type b (Hib)</td>
<td>1993</td>
<td>Until 2003 separately, subsequently in the form of DTP-polio-Hib</td>
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<tr>
<td>Meningococci C (MenC)</td>
<td>2002</td>
<td>Separately</td>
</tr>
<tr>
<td>Hepatitis B (HepB) - children at elevated infection risk</td>
<td>2003</td>
<td>Children with at least one parent from a country where the prevalence of hepatitis B carriership is &gt; 2%; in the form of DTP-polio-Hib-HepB</td>
</tr>
<tr>
<td>Pneumococci</td>
<td>2006</td>
<td>Separately</td>
</tr>
</tbody>
</table>

*a All children born after 1945 were invited for vaccination.
Developments in the programme

2.2 Changes in programme delivery methods and vaccine production

Clinics, CIb and municipal records

Delivery of the existing NIP is today part of the Basic Package of Child Healthcare Services and takes place at infant and toddler clinics all over the country. In 2005, the newly created Centre for Infectious Disease Control (CIb; part of the RIVM) was given responsibility for coordination and central control of the NIP. The NIP is funded through the system provided for by the Exceptional Medical Expenses Act (AWBZ); as such it is free at the point of delivery. The overall cost of the NIP is roughly 56 million euros a year: less than 10 per cent of the total amount spent on health promotion and protection and less than 0.15 per cent of all public health spending (table 4).

Each province, plus the cities of Amsterdam and Rotterdam, has its own vaccine registry, which is responsible for vaccine distribution and the associated administration. Data regarding the children to be invited for vaccination come from the General Municipal Register. The vaccine registries are informed by the municipal registries about all births and all relocations involving children covered by the NIP. Children are invited for vaccination at the ages indicated in table 2. If vaccination does not take place, a second invitation is issued, either in writ-
The provincial vaccine registries are automated.

| Table 3 Existing child healthcare contact schedule (simplified) |
|-----------------------------|-----------------------------|
| **Age** | **Setting** | **Other checks include:** | **Vaccination** |
| 4 to 7 days | Home visit | PKU and 13 other metabolic disorders, CHT, AGS, sickle-cell anaemia, screening for perceptive auditory impairment | - |
| 7 to 14 days | Home visit | General anamnesis, social environment, file creation | - |
| 21 to 28 days | Consultation | General anamnesis, congenital abnormalities, growth, assessment of contraindications for NIP participation | - |
| 7 to 8 weeks | Consultation | Growth | + |
| 3 months | Consultation | Developmental assessment, growth | + |
| 4 months | Consultation | Growth | + |
| 6 months | Consultation | Developmental assessment, growth | - |
| 7.5 months | Consultation | Dietary advice, motor control, speech/language development | - |
| 9 months | Consultation | Developmental assessment, growth, early detection of visual disorders | - |
| 11 months | Consultation | Growth | + |
| 14 months | Consultation | Developmental assessment, growth | + |
| 18 months | Consultation | Parenting issues, pedagogical observation, anticipatory information | - |
| 2 years | Consultation | Growth, speech and language, parenting issues | - |
| 3 years | Consultation | Speech and language, parenting issues, pedagogical observation, detection visual disorders | - |
| 3.9 years | Consultation | Growth, detection of visual disorders | + |
| 5 years | School | Screening for speech and language disorders | - |
| 5 years or primary school year 2 | School | Growth, interaction with other children, psycho-social development, emotional function, detection of visual disorders | - |
| 9 years | General | Growth, attitude problems, psycho-social development, emotional and social function, bullying/violence | + |
| 10 years or primary school year 7 | School | Growth, attitude problems, puberty, truancy | - |
| 13 years or secondary school year 2 | School | Growth, attitude problems, puberty, truancy | - |

The expectation is that responsibility for the registries will be transferred to the CIb in the course of 2007.

The CIb coordinates communication with the public and with clinic personnel. The media used include a website (www.rvp.nl) and an extensive series of leaflets providing information about the NIP, the target diseases and the vaccines. The leaflets are available in sixteen languages.

The CIb also acts as the national report point for suspected adverse reactions to vaccinations provided through the NIP. The data thus collected serve as the basis for passive monitoring of safety within the NIP. Safety is also actively monitored by specific research into adverse reactions. The CIb evaluates the effectiveness of the NIP by means of surveillance programmes for the target diseases.
The Netherlands Vaccine Institute (NVI) produces or buys in vaccines for the NIP. In many countries around the world, the production of vaccines for national vaccination programmes was initially handled by public health agencies. In most western countries, however, national vaccine producers have disappeared following a major wave of mergers. The motivation for the mergers was the cost burden of the necessary safeguards and the increasingly high cost of developing new vaccines. In the west, there are now just a handful of large producers of the basic vaccines given to infants. The Netherlands is one of the very few western countries that still have their own national vaccine production agencies.

The decline in the number of active producers means that capacity has also decreased. It is unlikely that capacity problems will ease in the near future, since the establishment of new factories requires a great deal of time, the profit margins are lower than those associated with other pharmaceuticals and the demand from developing countries is increasing all the time. In the USA and elsewhere, this situation has repeatedly led to the rationing of vaccines.

For many observers, the importance of retaining not only expertise in the fields of infectious disease control and vaccine preparation, but also adequate production capacity, has been re-emphasised as fears concerning bioterrorism have grown since the attacks of 11 September 2001 in New York and Washington. It was partly those events that prompted the Dutch government to establish

<table>
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<tr>
<th>Programme</th>
<th>Expenditure (millions of euros)</th>
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<tbody>
<tr>
<td>Breast cancer screening</td>
<td>43.0</td>
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<tr>
<td>Cervical cancer screening</td>
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<tr>
<td>Ante- and postnatal prevention</td>
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<tr>
<td>National Influenza Prevention Programme</td>
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<tr>
<td>National Immunisation Programme</td>
<td>55.9</td>
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<tr>
<td>Other, including STD clinics, FH screening</td>
<td>9.8</td>
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<tr>
<td>Behavioural health promotion</td>
<td>16.5</td>
</tr>
<tr>
<td>Prevention/detection of (non-)infectious disease</td>
<td>31.1</td>
</tr>
<tr>
<td>Accessibility and quality of public health care</td>
<td>192.5</td>
</tr>
<tr>
<td>Crisis and disaster coordination and response</td>
<td>6.8</td>
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<tr>
<td>Consumer and product safety</td>
<td>86.7</td>
</tr>
<tr>
<td>R&amp;D programming</td>
<td>100.4</td>
</tr>
<tr>
<td>Parent and child care/dietary advice</td>
<td>47.4</td>
</tr>
<tr>
<td>Total prevention and health protection expenditure</td>
<td>671.3</td>
</tr>
<tr>
<td>Total health care expenditure, including budgetary expenditure</td>
<td>44,642.4)</td>
</tr>
</tbody>
</table>
the Netherlands Vaccine Institute (NVI) by a Cabinet decision dated 1 February 2002.

The NVI was formed out of the vaccine development and production divisions of the RIVM and the Foundation for the Advancement of Public Health and Environment (SVM), which were thus separated from their former parent organisations. One of the NVI’s roles is to supply vaccines for the NIP, which it may do either by producing vaccines itself, or by buying them.

As previously indicated, the Committee regards the NVI as a key element of the nation’s public health infrastructure, both as a knowledge institute and a production facility. Nevertheless, the Committee has previously argued that the preparation of advice on choice of specific vaccines, the purchase of vaccines and the production of vaccines should be kept separate, with a view to preventing any conflict of interests.6

### 2.3 Variations in the vaccination rate

#### 2.3.1 High national vaccination rate

Through the Vaccination Act of 1939, the government of the day exerted considerable pressure on parents to have their children vaccinated against smallpox. However, it has always been one of the basic tenets of the NIP that parents should be free to decide whether to participate. A good public information programme and the comprehensive registration of vaccinations are therefore essential in order to attain the vaccination rates necessary to prevent infectious disease.

Acceptance of the NIP has been high since its inception. Medical Inspectorate data from 1955, before the existence of the NIP as such, indicate that roughly 56 per cent of children received the first three DTP injections. In 1960, by which time the NIP was operational, the figure had risen to 83 per cent.

In 1962, the DTP-polio combination vaccine was introduced, helping to push the vaccination rate up even higher. That year, 96 per cent of children received the first three injections, and 91 per cent also received the booster injection at eleven months. One of the main factors behind the high level of participation in the Netherlands is probably the link between the vaccination registries and the general population registers.

At present, the rate of primary DTP-polio-Hib vaccination among infants and the rates of MMR and meningococci C vaccination among toddlers are more than 95 per cent. The rate of booster vaccination against DTP-polio among toddlers and the rates of DTP and MMR vaccination among nine-year-olds are of a similar order (see table 5).
Nevertheless, the vaccination rate is not uniformly high across the country: there is considerable geographical variation. There is a diagonal band running across the country, from Zeeland in the south-west, through parts of South Holland, North Brabant, Utrecht and Gelderland to the northern part of Overijssel in the north-east, where the vaccination rate in many municipalities is considerably lower than the present national average of more than 95 per cent. In some of the municipalities concerned, the vaccination rate is actually less than 80 per cent (figure 1). What distinguishes the municipalities in question is relatively large pietistic reformed Christian communities. Some people in these communities have a conscientious objection to vaccination, which they perceive to be a denial of divine providence. Because of its similarity to the predominantly orthodox Christian area of south-eastern USA, the band of vaccination-averse municipalities stretching across the Netherlands is often referred to as the country’s bible belt.

There are other groups in the Netherlands that are averse to vaccination on moral or religious grounds. These include people with anthroposophical beliefs, who take the view that illness can strengthen the body and soul. Some anthroposophists therefore argue that a natural infection is preferable to vaccination.

Among some groups of well-educated parents (in what is sometimes referred to as the ‘canal belt’, because of the urban intelligentsia’s popular association with traditional canal-side townhouses) there is a belief that vaccination can sometimes be harmful to a child’s development. In this context, combination vaccines are a particular cause of concern. The possibility of immune system overload resulting from multiple vaccination is discussed in subsection 3.3. Vaccination-averse canal-belt and anthroposophical groups differ from communities that are opposed on orthodox Christian grounds, insofar as they do not generally live in clusters. The risk of an epidemic is therefore not as great in such groups, although problems can develop relatively quickly in anthroposophical schools.

Clusters of unvaccinated people in, for example, communities that are conscientiously opposed to vaccination are of great significance in the epidemiology of polio, measles and rubella in the Netherlands (see subsection Relationship between effectiveness and vaccination rate).
2.4 Impact on morbidity and mortality

2.4.1 Definitions

The NIP should ultimately be judged on its effectiveness: the extent to which vaccination reduces morbidity and mortality. In this context, it is important to distinguish between effectiveness and efficacy. Efficacy is a property of a vaccine, which is unrelated to the population in which it is used; it is an expression of the vaccine’s protective effect under ideal, experimental conditions. Under such conditions, the efficacy of a vaccine is the percentage by which the risk of infection among vaccinated people is reduced, relative to the risk among unvaccinated people. Efficacy is best measured in the context of a randomised placebo-controlled trial.

In practice, the effect of vaccination will normally be less positive than the efficacy of the vaccine might suggest. Effectiveness is an expression of what is actually achieved in the field. The effectiveness of vaccination can fall short of the efficacy of the vaccine used for various reasons. The (genetic) make-up of the population may differ from that in the study population, for example. The disease burden in the population may also be lower, or the vaccination schedule followed in practice may not be the same as that used in the study. In addition, the different components of a combination vaccine can negatively influence one another. Another problem that sometimes occurs is that in practice a relatively large number of people are late presenting themselves for primary or booster vaccinations, or do not present at all.
Developments in the programme

Figure 1  Municipal rates of DTP/DTP-polio, Hib and MMR vaccination in the Netherlands: percentages of infants fully immunised in the 1996, 2000 and 2002 cohorts. Source: RIVM and the National Association of Vaccination Registries.\textsuperscript{18}

D(K)TP = diphtheria, (whooping cough,) tetanus, polio
Hib = Haemophilus influenzae type b
BMR = mumps, measles, rubella
Table 5 Vaccination rates as at 1 January 2005, broken down by cohort and vaccination type (source: LVE and RIVM)\(^1\)

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>DTP-polio 11 mths</th>
<th>Hib 11mths</th>
<th>Men C 14 mths</th>
<th>Measles 14 mths</th>
<th>MMR 14 mths</th>
<th>DTP 4 yrs</th>
<th>MMR 4 yrs</th>
<th>aP 4 yrs</th>
<th>DTP 9 yrs</th>
<th>MMR 9 yrs</th>
<th>Rubella (girls)</th>
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x = Vaccination stopped
\(^1\) = Where the 1970s-1986 cohorts are concerned, the reference date is 1 September 1972-1988. Where subsequent cohorts are concerned, the reference date is 1 January, starting with 1 January 1990.

\(^2\) = Because regular vaccination was available to only some members of this birth cohort (those born after 1 June 2001), the figure quoted may be converted to a national rate of (12/7 x 56.2) 96.3 per cent. Corrected estimates of the rate of Men C vaccination among children aged twelve months to eighteen years are available from the National Public Health Atlas (www.zorgatlas.nl; search for ‘meningokokken C’). These figures include vaccinations administered in the context of the campaign and vaccinations previously administered by GPs. According to the Atlas, the rate of Men C vaccination among children aged twelve months to eighteen years was 94.1 per cent following the 2002 campaign\(^3\).

\(^3\) = The rise relative to the 1992 cohort is attributable largely to an administrative change. The definition of this variable applied in the provinces of Zeeland, South Holland and part of North Holland (Amsterdam) was changed in 2004 from ‘the number of nine-year-olds that have received two MMR vaccinations’ to ‘the number of nine-year-olds that have received at least the first MMR vaccination’. In the other provinces, the latter definition had always been used. If the three affected provinces are discounted, the rate of MMR vaccination among school children rose by 0.2 per cent in 2004, compared with 2003.
To establish how effective a vaccination programme is, one needs to perform a study under conditions that reflect actual field conditions as closely as possible. The object is not to determine the maximum effect, as with efficacy, but to accurately estimate the effect in practice. The established procedure is for the efficacy of a new vaccine to first be appraised by studying a group of subjects under controlled conditions. Ideally, the effectiveness of vaccination should subsequently be determined by studying the vaccine’s use in the target population, e.g. the population of the Netherlands. This is preferable because, unlike efficacy, effectiveness differs from one population to another. In practice, though, effectiveness is sometimes estimated on the basis of a study involving a comparable population.

However, the ultimate indicator is the actual infection rate in the population; change in this variable shows whether vaccination does in practice provide the protection sought. It is instructive to establish the effect of vaccination in terms of reduced mortality and disease burden. Data from various sources are available for this purpose: mortality data published by Statistics Netherlands, hospital admission data, infectious disease registration data and laboratory test data. Unfortunately, it is still more difficult to express effectiveness in quantitative terms in this context. The reason being that, in contrast with controlled study conditions, field conditions offer little scope for comparing the infection risk among vaccinated people with the risk among unvaccinated people.

2.4.2 Mortality reduction

So, what can be concluded from the available data with regard to the NIP’s effect on mortality in the population of the Netherlands? In the first half of the twentieth century, the NIP target diseases diphtheria, whooping cough, measles and meningococcal infections still were major causes of childhood mortality. Vaccines against these diseases became widely available from the middle of the twentieth century. By that time, overall rates of mortality and disease burden (which until the twentieth century were largely attributable to infectious disease) had already fallen considerably (see table 6). The main reasons for the established decline are likely to have been improved nutrition and housing, the general availability of safe (clean) drinking water and hygienic food production.

The use of vaccines in public programmes accelerated the decline in mortality and disease burden attributable to infectious disease in the second half of the twentieth century. The introduction of universal vaccination largely eliminated polio as a cause of death. Diphtheria deaths ceased following the introduction of mass DTP vaccination in 1953 (see figure 2), all later cases being imported.
Where whooping cough and tetanus are concerned, the influence of vaccination on mortality is less clear. These diseases were already strongly in decline before vaccination began, and their decline continued thereafter. Mortality from whooping cough fell from approximately a thousand cases a year at the start of the twentieth century to approximately a hundred by 1950 and thirty by 1955. Following the introduction of vaccination in 1957, whooping cough deaths were practically eliminated. However, a handful of deaths have been reported since 1995, mainly involving children who had not (yet) been fully immunised. Sporadic tetanus infections have continued to occur among unvaccinated or incompletely vaccinated people.

At the start of the twentieth century, mortality from measles was still more than 2,500 cases a year; following the introduction of vaccination in 1976, the number fell to just a handful of cases a year. The continuing fatal potential of measles, even in the Netherlands, was illustrated in 1999/2000, when an epidemic in an unvaccinated community claimed the lives of three children.


It is estimated that the introduction of universal vaccination against meningococci C infection in 2002 has prevented twenty deaths a year. The impact of vaccination against pneumococci, introduced in 2006, is not yet known, but it is expected to cut the annual number of child fatalities attributable to such infections by sixteen and adult fatalities by sixty-two.

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Table 6 Mortality per 10 000 children, by age groups per year, in the Netherlands 1860-1960 Source: 20.
2.4.3 Morbidity reduction

How has the NIP affected disease burden in the Netherlands? The programme’s impact on the individual diseases is summarised below.

Polio

Polio vaccination has had an unmistakable influence not only on mortality, but also on morbidity. In the first half of the twentieth century, there were several major nationwide polio epidemics. Since the introduction of universal vaccination, there have been only localised epidemics confined to unvaccinated religious communities: one in 1978 (110 cases) and another in 1992-1993 (seventy-one cases). The Netherlands has made international undertakings to do all it can to prevent such epidemics, since they can lead to the disease spreading elsewhere and thus undermine efforts to eradicate polio worldwide.
Diphtheria and tetanus

Diphtheria and tetanus are now almost unknown in the Netherlands. The introduction of universal vaccination has therefore virtually eliminated the disease burden associated with these conditions.

Whooping cough

Until 1976, doctors were not obliged to report cases of whooping cough. Consequently, it is difficult to assess the effect of whooping cough vaccination on the levels of morbidity associated with this condition. Furthermore, the data for the years after reporting became compulsory are not entirely transparent, partly because the condition’s definition has been revised several times. Nevertheless, it is probable that vaccination was very effective in the period up to the 1980s.

However, despite the high vaccination rate, whooping cough has remained an endemic disease in the Netherlands, with outbreaks once every few years. In the mid-1980s, following a reduction in the vaccine dose, there was an epidemic rise in case numbers. Several further whooping cough epidemics have occurred since the mid-1990s. These epidemics are attributable to a reduction in the effectiveness of the vaccine used in the Netherlands, coupled with the particular properties of that vaccine and the circulation of bacterium strains that differ from those used to make the vaccine.

A new acellular whooping cough vaccine was therefore introduced in 2005, following the success of a similar vaccine that had been given to four-year-old children since 2001. Unfortunately, the protection afforded by vaccination against whooping cough lasts only six to eight years. Consequently, older children and adults play a role in enabling the bacteria to remain in circulation. It is not presently clear how very young infants (for whom the disease is most dangerous) can be protected. Therefore, following the Committee’s interim report on whooping cough vaccination, a study has been set up, to gather information about the sources of infections contracted by such very young infants. The results of this study are due for publication at the end of 2007.

Measles, mumps and rubella

Where measles, mumps and rubella are concerned, vaccination has again had a clear effect. Since the introduction of universal vaccination, the annual number of measles cases occurring in the Netherlands has fallen to less than one per mil-
lion of the population. The incidence of the disease is lower in the Netherlands than almost anywhere else in Europe. Nevertheless, epidemics continue to occur in unvaccinated communities roughly once every five to seven years. The last such event was the epidemic of 1999-2000, when nearly 3300 cases of the illness were recorded.

The disease burden associated with rubella has also been substantially reduced. Following the introduction of universal vaccination for both girls and boys in 1987, the annual number of hospital admissions required in connection with congenital rubella syndrome went down from forty in 1980 to an average of less than one. Between September 2004 and September 2005, however, there was a rubella epidemic, affecting mainly people who had declined vaccination on religious grounds (see figure 3). As far as can be discerned, thirty-two pregnant women were infected. Fifteen of the women concerned went on to have babies with congenital rubella infection (CRI), nine of whom had congenital abnormalities that may be associated with congenital rubella syndrome. There were also two cases of intrauterine foetal death.

Prior to the introduction of universal vaccination against mumps in 1987, between three hundred and eight hundred children a year were being admitted to hospital with mumps-related meningitis. Such admissions are now required only occasionally. Nevertheless, in 2004 and 2005 a number of breakthrough infections involving a special variant of the virus occurred among vaccinated secondary school pupils.

Hib

Following the introduction of vaccination against invasive *Haemophilus influenzae* type b (Hib) infections in 1993, the number of such infections fell sharply, from roughly seven hundred a year to a minimum of twelve in 1999. Since then, however, the number has edged up again to forty-nine in 2004. This may be due to a reduction in the number of natural re-infections. In the past, natural re-infections helped to maintain the level of immunity in the population. However, the universal vaccination of infants has led to a gradual reduction in the number of carriers, which may now be resulting in a lower level of immunity in the population.

A similar pattern has been seen in the UK: following a sharp initial decline, the number of Hib cases reported is now rising. One of the factors that have contributed to this phenomenon has been the introduction of an acellular whooping
cough vaccine. The point being that the cellular whooping cough vaccine previously in use had the effect of reinforcing Hib vaccination. However, the fact that in the UK booster vaccinations were not until recently given to infants around the age of twelve months has probably been more significant. Intriguingly, there has been no recovery in the Hib infection rate in Finland, where vaccination has been the norm for more than eighteen years.

Figure 3 Laboratory-confirmed cases of rubella in the Netherlands, 1-9-2004 to 13-9-2005 (Source: Osiris).
The Committee concludes that Hib vaccination is effective, but believes that further research is necessary into the question of long-term protection and into interactions with other vaccinations.

Meningococci C

The 2002 introduction of vaccination against meningococci C infections was followed by a sharp decline in the number of invasive infections by this pathogen. In 2001, there were 276 reported cases; in 2005 there were just four, all involving older unvaccinated people. On the grounds of cost, it was decided to work on the basis of a single vaccination at the age of fourteen months (plus a ‘catch-up’ programme for all children up to and including eighteen-year-olds). This decision has proven to be the right one, since there have been no breakthrough infections in the Netherlands, in contrast to countries where vaccination has been provided at an earlier age.  

Hepatitis B

The NIP has two target groups for hepatitis B vaccination: 1) children whose mothers carry the virus and 2) children with at least one parent from a country where the prevalence of hepatitis B is endemic. Where the first group is concerned, vaccination is used as a form of post-exposure treatment. Without treatment, such children are very likely to acquire chronic infections like their mothers. This in turn would mean that in due course they were liable to pass the virus on to their families and sexual partners. In the long term, chronic hepatitis B infection brings a risk of liver cirrhosis and liver cancer. Vaccination has been provided for this first target group since 1989, but was formally incorporated into the NIP only in 2003. It is believed that the programme prevents around two hundred infections and 180 carrier cases every year. Where the second target group is concerned, vaccination is purely preventive. The children in this group are at increased risk of social contact with carriers and thus of infection. Models have indicated that, without vaccination, there would be between 1150 and 2550 infections a year in the population as a whole, ninety to 220 of which would become chronic and result in carrier status. Some 27 to 36 per cent of carriers would be less than fifteen years old. Vaccination has largely eliminated infection within the target group.
Pneumococci

Because vaccination against pneumococci was introduced only recently, its effects are not yet known. Nevertheless, the Health Council has previously estimated that fifty-six cases of meningitis, 103 cases of sepsis, 1800 cases of pneumonia and 52 000 cases of otitis media will be prevented annually among children up to ten years old. It is also believed that vaccination will prevent twenty-nine cases of meningitis and 205 cases of sepsis in other children and adults a year.3

2.4.4 Relationship between effectiveness and vaccination rate

It is known that, if vaccination rates fall below about 90 to 95 per cent, epidemics of various NIP target diseases are liable to occur. Since 1990, the Netherlands has seen epidemics of polio (1993), measles (1999-2000) and rubella (2004-2005) in communities that are averse to vaccination on conscientious grounds. The polio epidemic involved seventy-one cases of the disease, and two fatalities. In the measles epidemic, there were 3292 cases of the disease and three deaths. The rubella epidemic is described in subsection 2.4.3.

Clusters of unvaccinated people, such as communities that are averse to vaccination on conscientious grounds, have become very important in the epidemiology of polio, measles and rubella in the Netherlands. Because such communities maintain contacts with similar groups in other countries, there is a risk of a pathogenic micro-organism being (re-)introduced to this country. Conversely, polio, measles and rubella have been passed from epidemic-hit orthodox communities in the Netherlands to associated communities abroad, including Canada. Such international communication of disease is an obstacle to the general eradication of polio and measles.

There is reason to fear that epidemics will continue to affect vaccination-averse communities from time to time in the future. In the event of such an epidemic, there is a danger of the virus in question passing to other vulnerable population groups. During the measles epidemic that hit vaccination-averse communities in 1999-2000, for example, cases were reported in the mainstream population, involving children who had yet to receive the vaccine.

2.5 Safety

Like vaccine efficacy, vaccine safety should ideally be assessed in well-designed, controlled and randomised trials. Typically, efficacy and safety are studied in
Developments in the programme 45

combination, as part of the licensing process. Various methodological pitfalls exist in the field of vaccine safety research, which can lead to the underestimation or overestimation of adverse reaction frequency and seriousness.\textsuperscript{25,26} In some cases, postmarketing surveillance by means of a system for registering adverse reactions associated with licensed vaccines can be an alternative to extensive trials, particularly where rare adverse reactions are concerned.

The Netherlands has a system for registering adverse reactions to the vaccines used in the NIP. The register is maintained by the CIb, which produces annual reports on the reactions reported to it.\textsuperscript{27} However, adverse reactions can also be reported to the registrant (the manufacturer) or to the Netherlands Pharmacovigilance Centre LAREB (www.lareb.nl). Medical practitioners are being actively encouraged to report adverse reactions to the RIVM/CIb. Meanwhile, arrangements have been made with LAREB for the exchange of incident report data.

A registrant has a statutory obligation to report adverse reactions to the Medicines Evaluation Board (MEB). Adverse reactions reported to the MEB are assessed at the European level. This can lead to revision of the product information or, in serious cases, to revocation of the product’s registration. In this context, the definition of a serious adverse reaction used by the European Agency for the Evaluation of Medicinal Products (EMEA, www.emea.eu.int) applies, namely a reaction leading to death, hospitalisation, prolonged hospitalisation or permanent invalidity.

Because nearly all young children are vaccinated several times, and the symptoms and conditions involved in adverse reactions can have causes other than vaccination, considerable expertise is required to decide whether a reported phenomenon is actually vaccine-related.

The Committee regards the adverse reactions register as very important, but also wishes to make the point that it has shortcomings. Registration is passive: data is recorded only if someone takes the initiative to report it. It may be assumed that almost all serious conditions developing after vaccination are recorded. However, it is likely that many minor or transient (but nevertheless unpleasant) post-vaccination phenomena are not reported.

Since 2004, the CIb has also been undertaking active targeted research into the frequency of adverse reactions. Such research serves several purposes: 1) it provides reliable data on minor and transient post-vaccination phenomena, 2) it provides insight into how complete passive registration is and 3) it enables particular questions to be addressed, such as how switching to another vaccine affects the frequency and nature of adverse reactions.
There is no generally accepted international system for classifying adverse reactions. Nor is there unanimity as to which post-vaccination phenomena should be considered serious.

In the absence of a generally accepted system for classifying adverse reactions by seriousness, the Committee put forward its own classification system in an earlier report on vaccination against whooping cough. Under this system, a ‘serious adverse reaction’ is defined as one entailing death, serious neurological phenomena or permanent physical injury. The Committee also defined a category entitled ‘very disquieting adverse reactions’, consisting of adverse reactions which result in no permanent physical harm, but which can be very disturbing or disagreeable for a child or its parents. This category includes febrile convulsion, collapse and persistent crying. All adverse reactions that cannot be placed in either of the first two categories are classed as ‘other adverse reactions’. Such reactions include injection site phenomena (e.g. pain, swelling or inflammation), (high) fever, malaise, loss of appetite, vomiting, drowsiness and sluggishness.

Vaccinations administered within the NIP rarely or never cause serious adverse reactions. Nor do they often result in ‘very disquieting adverse reactions’. ‘Other adverse reactions’ are relatively common, however. Adverse reactions of the latter two categories were reported relatively often following administration of the cellular whooping cough vaccine. Since the switch to an acellular whooping cough vaccine in 2005, there has been a substantial reduction in the total number of suspected adverse reactions.

Until recently, the Health Council’s Committee on Adverse Reactions to NIP Vaccinations reviewed the RIVM’s assessment of reported serious or unusual phenomena and of all phenomena with permanent implications. In its most recent report, relating to the years 2002 and 2003, the latter committee concluded that the number of adverse reactions to NIP vaccinations was small. More than two and a half million vaccinations were administered, following which there were seventy-four reports of suspected adverse reactions, which – in accordance with the predetermined criteria – were referred to the committee (sixty-two disease cases and twelve fatalities). In forty-two of the sixty-two reported cases of disease, the Health Council concluded that an association between vaccination and the disease phenomena was improbable. A link was considered possible in fifteen cases and probable in five. In these twenty cases, the children recovered from their adverse reactions. In the cases where death followed vaccination, the Committee determined that six were unrelated to vaccination, and five probably unrelated. In one fatal case, the Committee made no judgement due to lack of data. However, the information that was available was not suggestive of an asso-
ciation. In total, therefore, there were twenty cases of serious but transient problems possibly or probably associated with vaccination. Responsibility for the review and assessment activities described above has now been transferred to an external expert committee at the RIVM, with effect from the 2004 reporting round.

2.6 Selection of target groups

2.6.1 The original target group: children

The NIP is a public programme for tackling childhood diseases, which has developed out of existing activities in the field. There are good reasons for the NIP’s existing focus on the vaccination of children:

1. Many conditions can first appear in childhood or are exclusive to childhood. These so-called childhood diseases are precisely the diseases against which it is possible to develop effective immunity, naturally or through vaccination.

2. A good vaccination programme aimed at children offers the greatest organisational scope for achieving a high vaccination rate. A high vaccination rate is important for the establishment of herd immunity.

Herd immunity is the phenomenon that enables people who have not acquired immunity through natural infection or vaccination to nevertheless enjoy a degree of protection, on account of living among other people who are immune. In other words, herd immunity reinforces the effect of vaccination, resulting in a greater overall effect than might be expected from the number of vaccinated people in a population.

Indeed, if a vaccination provides prolonged or lifelong resistance, the related condition may be eliminated without absolutely everyone being vaccinated. Where mumps, measles and rubella are concerned, for example, a vaccination rate of between 90 and 95 per cent is sufficient to prevent the disease spreading. Since the vaccination rate in the Netherlands is at the necessary level, these diseases are being adequately suppressed by the universal vaccination of children.

Herd immunity is relevant only in the context of diseases that are transmitted from human to human; it does not come into play where tetanus is concerned, for example. Another criterion for effective herd immunity is a fairly uniform vaccination rate distribution.

Although, as indicated earlier, other factors have also played a role, the vaccination of children has made an important contribution to the near-elimination of many diseases. Because of the special importance attached to the protection of

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children, it should be possible to give the improvement of an existing vaccination for young children priority over the introduction of a new vaccination for other age groups.

2.6.2 Possible extension of the programme to cover other groups

So far, the NIP has focused primarily on childhood diseases. In recent years, however, its scope has increasingly been widened to include other groups.

Should adults be vaccinated against whooping cough?

If the protection provided by vaccination is not very long-lived, or if the vaccination rate is not high enough, a disease can continue to circulate in the population despite the vaccination of young children. Thus, a childhood disease can develop into a condition that also threatens adult health.

Whooping cough is one such disease: prior to the introduction of vaccination against the illness, almost everyone would have been infected by the bacterium from time to time. Provided that the interval between infections was not too great, the individual’s resistance would be boosted on each occasion, so that he or she always retained a degree of immunity. Since the introduction of universal infant vaccination, the bacterium has not been able to circulate as easily as before, with the result that older children and adults come into contact with it less frequently. Their resistance is consequently lower than previous generations’ and they are therefore more likely to develop full-blown whooping cough when exposed to the bacterium.

In older children and adults, the disease is generally much less serious than in small children, its chief symptom being a chronic cough. However, adults with whooping cough can infect others, including infants who are not yet fully protected by vaccination. It is not until several months after the first injection that an infant has full immunity, and very young infants are therefore at greater risk of infection.

Hence, the existing policy of vaccinating at the ages of two, three, four and eleven months cannot effectively protect all children up to the age of five against whooping cough. To provide comprehensive protection for small children and to control whooping cough in the adult population, everyone should be vaccinated periodically – say, every ten years.

The Health Council accordingly recommended undertaking research into the sources of infection in very young infants, and a study has now been started. The expectation is that the study findings will provide a basis for the development of
efficient strategies for the revaccination of older children and adults. Therefore, once the study has been completed, the Council anticipates making recommendations concerning additional measures to protect very young infants. One option is the targeted vaccination of people who come into contact with infants who have yet to acquire full immunity, such as babies’ parents, grandparents and other family members, plus nursery staff and health workers.6

Should older people be revaccinated against diphtheria and tetanus?

With some diseases, although circulation of the pathogenic bacterium or virus is prevented, there is still a risk of reintroduction from a country where the disease remains endemic. Where such diseases are concerned, it is pertinent to ask whether the protection provided by vaccination is sufficiently long-lived for the adult population to be safe from the disease. May an individual member of the public expect lifelong protection from the vaccinations provided through the NIP? Is lifelong protection provided against some conditions but not others? And should adults be revaccinated against certain conditions?

The Health Council has previously reported on the systematic vaccination of older people.30 Its conclusion was that the general revaccination of adults against diphtheria and tetanus is not necessary. Following vaccination, the average person is protected for at least twenty and twenty-five years, respectively. As things stand, the associated risks are not sufficient to justify general revaccination. However, the position may change over time. Furthermore, the risk-benefit balance may be different for individuals in certain groups, such as people travelling through or staying in countries where NIP diseases are still endemic.

Should older people be vaccinated against influenza and shingles?

As explained above, declining adult immunity associated with the vaccination of young children can in some cases make it appropriate to consider revaccinating adults. Under certain circumstances, it is desirable that a public vaccination programme should not focus exclusively on children or prioritise the treatment of children. For there are vaccines that can make an important contribution to public health through adult administration. In this context it is also important to consider the effects of aging on both innate and acquired immunity.31-33

Consider, for example, influenza vaccination, which is provided through a national programme. Although the National Influenza Vaccination Programme is not part of the NIP, but is organised separately through GPs, its objective is con-
sistent with that of the NIP. Influenza vaccination is provided to various groups, including older people.

It is expected that before long a shingles vaccine will be available, which could also be given to older people. The Health Council has previously reported on another supplementary form of vaccination for older people (polysaccharide vaccination against pneumococcal infections) and decided not to recommend its introduction. However, the disease burden associated with pneumococcal infections is considerable and a conjugated pneumococcal vaccine may in the future become available for use against this group of viruses.

The Committee anticipates that older people will increasingly become a target group for public vaccination programmes. Because immunity tends to decline with age, various illnesses are particularly problematic for older people, much as they are for children, whose immune system is still developing. Examples include whooping cough and respiratory syncytial virus infections.

**Should adolescents be vaccinated against STDs?**

Various vaccines against sexually transmissible diseases (STDs) are now coming onto the market. A vaccine against hepatitis B is already available, and a vaccine against human papilloma virus (HPV; an important precursor of cervical cancer) was registered in 2006. In due course, vaccines may well become available against herpes simplex virus type 2 (HSV-2), *Chlamydia trachomatis*, gonorrhoea and HIV. As such vaccines appear, it will increasingly be necessary to consider their inclusion in the NIP.

In 2001, the Health Council advised against universal infant vaccination against hepatitis B. On the Council’s advice, it was decided that such vaccination should be provided only to children with at least one parent from a country where hepatitis B remains prevalent. The vaccination provided is intended to prevent horizontal, non-sexual transmission of the virus from carriers to young children, in the context of intensive domestic contact.

Most hepatitis B infections acquired later in life are the result of sexual contact or the sharing of needles and other equipment by injecting drug users. Such communication of the virus could be prevented by vaccinating people in early adolescence (around the age of eleven or twelve). The existing vaccination scheme does not, however, provide for the treatment of youngsters at that age. The Health Council is due to report on the desirability of vaccinating all preadolescents against hepatitis B.
It is now also possible to prevent human papilloma virus (HPV) infection by vaccination. HPV infection can lead to the development of cervical cancer. Again, the availability of this vaccine raises the question of whether vaccination at the age of about eleven or twelve should be included in the NIP.

Should therapeutic vaccination be provided?

So far, the NIP has been geared primarily to preventive vaccination against infectious disease. However, it is likely that in the future vaccines against non-infectious diseases will also become available. Work is presently in progress with a view to developing vaccines against, for example, insulin-dependent diabetes mellitus, multiple sclerosis, melanoma and rheumatoid arthritis. The intention is that these vaccines will be for the treatment of people already suffering from the conditions in question. In other words, vaccination will be employed as a form of therapy.

The Committee takes the view that the therapeutic use of vaccines is not consistent with a general public programme for the prevention of disease, such as the NIP. Similarly, prospective vaccines intended to support a given form of behaviour, such as giving up smoking, are considered to have no place in the NIP. If and when vaccines of these kinds become available, their use should be an individual matter.

2.7 International cooperation

Infectious diseases do not respect international borders. Yet public health policy in Europe – both generally and in the particular field of infectious disease – remains largely a national matter. Nevertheless, the European Centre for Disease Prevention and Control (ECDC), a Stockholm-based agency of the European Union, began operating in 2005. The ECDC’s role is to support efforts to combat infectious disease in Europe. Priority is given to infectious disease surveillance, with a view to identifying epidemics as early as possible, but the ECDC also assists member states with outbreak management as necessary.

The Centre takes an interest in vaccination, but the harmonisation of national vaccination programmes remains a long way off. In the context of an earlier European project, the Statens Serum Institut in Copenhagen established an electronic network for vaccination in the European region (www.euvac.net). The network’s website also provides information about the various national vaccination schemes, from which some notable differences are apparent. To some extent the differences between national vaccination schemes reflect disparities in the distri-
The future of the National Immunisation Programme: towards a programme for all age groups

The emergence of disease. However, they are also a product of cultural differences and variation in the way national vaccination programmes are organised.

In 2006, the Federation of the European Academies of Medicine (FEAM) started a project concerned with the vaccination of humans and animals in the European Union (www.feam.eu.com). The objective of the project is to promote effective use of the potential of vaccination within Europe and to seek a degree of international alignment. Because of the international differences that exist, the harmonisation of vaccination schemes is not an option, but optimisation is nevertheless desirable.

2.8 Conclusion

A national vaccine institute remains important

The scope of the National Immunisation Programme has widened considerably over time. In 2005, responsibility for coordination and central management of the programme was transferred to the Centre for Infectious Disease Control (Dutch initials: CIb), part of the National Institute of Public Health and the Environment (RIVM). The Netherlands Vaccine Institute (NVI) produces or sources the vaccines used for the NIP. As previously indicated, the Committee regards the NVI as a key element of the nation’s public health infrastructure, both as a knowledge institute and a production facility. Nevertheless, the Committee believes that the preparation of advice on vaccine inclusion, the purchase of vaccines and the production of vaccines should be kept separate.

A high vaccination rate is necessary for effective disease control

Application of the principle that parents should be able to decide whether their children are vaccinated, the use of combination vaccines and linkage of the vaccine registries to general municipal registers have all probably contributed to the high vaccination rate achieved by the NIP since the outset. At present, more than 95 per cent of all children receive the full sequence of primary DTP-polio-Hib and MMR vaccinations, and DTP-polio, DTP and MMR booster injections. However, the vaccination rate is not uniformly high; significant geographical variations exist. In various municipalities with relatively large pietistic reformed Christian communities (some of whose members are averse to vaccination on conscientious grounds), the vaccination rate is considerably lower than the national average.
Despite vaccination rate variance, NIP is very effective

The NIP makes a major contribution to the prevention of childhood morbidity and mortality. The success of the NIP is one of the reasons that serious infectious childhood diseases have largely disappeared from the Netherlands. Complete eradication of most NIP target diseases is not possible, partly because of the presence of sizeable vaccination-averse population groups living in clusters. Such clusters of unvaccinated people have become very important in the epidemiology of polio, measles and rubella in the Netherlands. There is reason to believe that epidemics will continue to affect the communities in question from time to time. Furthermore, such epidemics can lead to the spread of disease to other population groups.

Registration of and research into adverse reactions remain important

The Netherlands has a passive system for the registration of adverse reactions to vaccination in the context of the NIP. The Committee regards this registration as very important, but also wishes to highlight its limitations. Since 2004, the frequency of adverse reactions has also been actively studied. Such research serves several purposes: 1) it provides reliable data on minor and transient post-vaccination phenomena, 2) it reveals the extent of passive registration and 3) it enables more specific questions to be addressed.

Vaccinations administered within the NIP rarely or never cause serious adverse reactions, i.e. death, serious neurological phenomena or permanent physical injury. Few very disquieting but transient adverse reactions are reported either. Other adverse reactions – injection site phenomena (e.g. pain, swelling or inflammation), (high) fever, malaise, loss of appetite, vomiting, drowsiness and sluggishness – are relatively common. Disquieting but transient adverse reactions and other adverse reactions were relatively common in association with the cellular whooping cough vaccine previously used in the NIP. Since the switch to an acellular whooping cough vaccine, in 2005, the number of suspected adverse reactions reported has fallen sharply.

NIP to focus on additional target groups

The NIP was originally set up to tackle childhood diseases and continues to focus primarily on the vaccination of children. However, various factors mean that the programme is likely to develop increasingly into a programme for all ages. The
probable drivers of such change include the role that older children and adults appear to play in the spread of certain pathogens, declining immunity among adults, the development of vaccines intended specially for older people, and the availability of vaccines against STDs.
3.1 Early vaccine development

Birth of the discipline

In 1798, Jenner published his classic work *An Inquiry into the Causes and Effects of Variolae Vaccinæ, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of the Cow Pox.* Jenner had investigated the belief, by then long established amongst farmers, that a person who had been infected with cowpox was resistant to the human disease of smallpox. In his *Inquiry*, he presented evidence to support what the farmers said. More significantly still, he reported an experiment, which involved taking infectant from a sore on the hand of Sarah Nelmes, a milkmaid, and transferring it to the arm of an eight-year-old boy named James Phipps, who subsequently proved to be resistant to smallpox. In this way, Jenner demonstrated that protective cowpox material could probably be transferred from human to human. His discoveries are generally regarded as the foundation of immunology and the scientific use of vaccination.

Inoculation – applying pus or crust material from a *human* smallpox sore to or under the skin of someone without the disease – had by that stage been used for centuries in China, India, Persia and Turkey. Lady Mary Wortley Montagu
encountered the technique, known as variolation, in Constantinople and intro-
duced it to England in 1721. It was known that someone inoculated with human
cowpox in this way was often resistant to the disease. The disadvantage of the
approach was, however, that a person thus inoculated constituted a risk to others,
because they could pass the disease on to them. Inoculated people therefore actu-
ally needed to be isolated. Jenner’s method made this unnecessary, since it
involved using not the human smallpox virus, but the related, less virulent cow-
pox virus.

Jenner used a human subject for his experiment, but Wouter van Doeveren,
Petrus Camper and Geert Reinders had several decades earlier experimented
with inoculation against rinderpest in Groningen. In the eighteenth century,
rinderpest regularly decimated the Netherlands’ cattle herds. A way of prevent-
ing the disease was urgently needed, because it was fatal in 80 to 90 per cent of
all cases. To begin with, the experiments were not very successful, but Geert
Reinders displayed great perseverance in continuing with the research. Under-
standing of the process was systematically increased in successive experiments.
In 1770, Reinders concluded that: 1) cattle not previously exposed to the disease
always became ill when inoculated, 2) cattle made even slightly ill by inoculation
were subsequently resistant to the disease when exposed to it naturally, and 3) the
method of inoculation and other therapeutic measures had barely any influence
on the outcome.

In 1774 Reinders made a breakthrough: he demonstrated that young calves
could be effectively immunised using living infectant under the cover of passive
immunity, transferred via colostrum or beestings* from a mother cow that had
recovered from the disease and was thus immune. In 1776 he published his
Waarneemingen en proeven meest door inëntinge op het rundvee gedaan,
dienende ten bewijze, dat wij onze kalvers van gebeterde koejen geboren, door
inëntinge tegen de veepest kunnen beveiligen (Observations and Experiments,
Mostly Involving the Inoculation of Cattle, Serving as Evidence that We Can Pro-
tect Calves Born to Recovered Mothers against Rinderpest by Inoculation).
Petrus Camper subsequently disseminated what had been learnt by delivering
lectures at the Société Royale de Médecine in France and the Berlin Gesellschaft
Naturforschender Freunde. Like Jenner, Camper was a member of the Royal
Society of Physicians in the UK.

It is therefore quite possible that Jenner was familiar with what had been
achieved in the Netherlands. Reinders’ method involved inoculation using essen-
tially unmodified pathogens. The great step forward made by Jenner was the use

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* Beestings are the first milk produced by a mammal after giving birth.
of a related pathogen – the less virulent cowpox virus – to provide immunity against a human disease, smallpox. Jenner is therefore generally regarded as the father of vaccination.

Nevertheless, it was Reinders who first described in detail the phenomenon of transient passive immunity based on maternal antibodies. He also demonstrated the value of repeated inoculation as a means of stimulating an effective immune response. Reinders’ work also showed that inoculation under the protection of maternal antibodies was safe and could lead to active immunisation. So there are good reasons for seeing Reinders and Jenner as the founders of immunology and the scientific use of vaccination.35-37

New methods

Louis Pasteur subsequently developed the principle of vaccination by means of an attenuated living micro-organism. In 1880, he published the findings of experiments involving a culture of cholera bacteria, which had been left to stand for an extended period. When the bacteria were given to chickens, not only did the birds survive, but they proved to be resistant when subsequently exposed to a particularly deadly strain of the disease. Shortly afterwards, in 1885, Pasteur performed a series of experiments using a chemically attenuated rabies vaccine. The work provoked fierce protest, since by vaccinating a subject with an attenuated living virus, he ran the risk of giving the person in question a fatal disease.

The next step was the development of inactivated vaccines. The groundwork for this advance was done by Daniel Elmer Salmon and Theobald Smith in the USA and by Charles Chamberland and Emile Roux at the Pasteur Institute in France. The two research groups published their findings in 1886 and 1887, respectively. Inactivated vaccines against typhus, cholera and bubonic plague became available in 1896 and 1897.

By the latter part of the nineteenth century, the foundations had been laid for modern experimental vaccinology. In this period, science also began to form an understanding of the specific association between receptors and antibodies. Furthermore, methods were developed for using dyes to reveal the presence of particular micro-organisms and to count antibodies. These techniques were refined in the first half of the twentieth century. The period 1875 to 1930 saw the development of an attenuated living vaccine against tuberculosis, an inactivated vaccine against whooping cough and protein-based vaccines against diphtheria and tetanus. The tissue culture and cell culture of viruses ushered in a new period of rapid development in the second half of the twentieth century (see table 7).
Towards a scientific approach

The gradual development of vaccinology from an entirely empirical discipline in about 1700 to a science based on understanding of how the immune system works is an ongoing process. Various sophisticated techniques are available to the modern vaccine developer. These include DNA techniques (genomics), protein-chemistry techniques (proteomics), ICT-based techniques for the analysis of micro-organisms in the search for antigens suitable for use in a vaccine, and recombination techniques for use in the production of antigens. Yet scientific insight into the underlying immunological processes remains far from complete. Most traditional vaccines are made either from intact viruses that have been inactivated or are living but attenuated, or from complex bacterial proteins. Ideally, a vaccine should contain only those proteins that will trigger exactly the right B cells, T helper cells and cytotoxic T cells and enable the acquisition of an adequate immunological memory. In many cases, however, not enough is known about the immune system for scientists to determine what components a vaccine should contain.

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Table 7. Vaccines used or with the potential for use in the Netherlands in the context of public health protection, arranged by type and year of initial availability.

<table>
<thead>
<tr>
<th>Attenuated living</th>
<th>Inactivated, whole organism</th>
<th>Protein/polysaccharide</th>
<th>Genetic engineering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox (1798)</td>
<td>Typhus (1896)</td>
<td>Diphtheria (1923)</td>
<td>Hepatitis B (recombinant, 1986)</td>
</tr>
<tr>
<td>Shingles (2006)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To: "Hib=Haemophilus influenzae type b; BCG=Bacille Calmette-Guérin"
Broadly speaking, science is capable of producing a vaccine for any condition to which prolonged immunity can be acquired in the event of natural infection. It has so far proved much more difficult to develop vaccines against conditions to which only limited natural immunity can be acquired, such as malaria and tuberculosis. The greatest challenge is the development of vaccines against diseases that are caused by micro-organisms capable of compromising the acquisition of immunity, such as HIV. Real progress in the fight against such diseases depends on building up greater fundamental understanding of the working of the immune system.

3.2 Interaction between immune systems

Improved understanding of immunological processes is needed if progress is to be made in the development of new vaccines against various types of disease. A number of recent discoveries concerning the working of the immune system promise to be of great significance in this context.

Innate and acquired immunity

Broadly speaking, the immune system may be divided into two compartments. First, there is the innate immune system, which is in place at birth and performs a number of general antimicrobial functions that are more or less the same in everyone. Second, there is the much more complex acquired immune system, which provides an antigen-specific immune response to exposure. The role of the innate immune system is to halt the progress of a pathogen by means of an immediate immune response. By contrast, the acquired immune system may take days or even weeks to develop an appropriate response.

Humans are born with relatively well-developed immune systems, but the body’s ability to build up resistance to specific antigens is quite limited at birth. This ability develops particularly rapidly in the first six months of life, but the immune system may go on learning throughout a person’s life. Before and immediately after birth, the T lymphocyte system reacts primarily by making T_{helper2} cells (Th2 cells). Th2 cells are white blood cells that make special messenger proteins (cytokines), thus triggering plasma cells to produce antibodies. In this phase of life, protection against infectious disease is based mainly on antibodies passed on by the mother.

In the postnatal period, however, there is a rapid shift, until a balance is reached between Th2 cells and T_{helper1} lymphocytes (Th1 cells). Th1 cells are another type of white blood cell, also known as inflammation-promoting T cells.
They are necessary for the acquisition of cellular immunity and the inactivation of bacteria by phagocytosis. The immune system is probably unable to make the Th1-switch entirely autonomously; it is believed that contact with micro-organisms plays a role via the innate immune system, including the Toll-like receptor system. If the Th2 cells remain dominant, a person is liable to develop allergies, while an over-active Th1-system may predispose a person to autoimmunity. Such imbalances may be related to exposure to micro-organisms and parasites, which influence the Th1 and Th2 control systems. It now seems that such exposure is important not such much as a means of stimulating the Th1 or Th2 system, as previously supposed, but as a means of regulating a balance between the two systems.

It also appears that there is a third system, in which interleukin-10 and T-regulator cells play a role, whose function is regulatory. The existence of such a system may explain why high levels of exposure to worm infection in large parts of the non-western world does not generally lead to allergy, even though such infections cause Th2 preponderance (see figure 4). 39,40
Interaction between innate and acquired immunity

The most exciting developments currently taking place in immunology perhaps involve our understanding of the innate immune system and its interaction with the acquired immune system. It appears that the response of the innate immune system influences the quality of the acquired immune response. Stimulation of the innate immune system by bacterial substances, such as lipopolysaccharide (LPS), CpG-DNA and heat shock proteins, seems to result in a more effective and better-regulated immune response.

Apparently, the cells that present antigens to the acquired immune system’s B and T lymphocytes (antigen-presenting cells or dendritic cells) have receptors for various bacterial and viral products. Depending on the type of product concerned, various of these so-called Toll-like receptors are activated. This in turn triggers the production of numerous interleukins and other messenger proteins. This system of receptors and interleukins enables fine regulation of the immune response by B cells (antibody production) and T cells (cellular immunity). By stimulating this system, bacterial products can have an adjuvant (enhancing) effect on certain antigens, or may even be essential for effective immune response. This discovery is consistent with the practical observation that, for example, mycobacterial extracts can strongly promote T and B cell response to antigens.

Interaction between the two systems has evolved over millions of years. It seems increasingly likely that the innate and acquired immune systems are minutely aligned with one another. This alignment probably also plays a role in maintenance of the balance between immunity, allergy and autoimmunity: the expressions of a single, complexly regulated immune system. Immunity involves an adequate and proportionate response to foreign bodies. Allergy entails overreaction to antigens originating outside the body that do not normally provoke an immune response. Autoimmunity involves response to the body’s own antigens, which are ordinarily tolerated.

Ideally, the immune system responds adequately, without allergy or autoimmunity. It is probable that realisation of this ideal depends partly on harmonisation of the various groups of T lymphocytes, the T helper cells (Th cells). The innate immune system appears to be an essential part of the general immune complex and to contribute to the maintenance of a proper balance between immunity, allergy and autoimmunity. This discovery promises to be highly significant in the development of a new generation of vaccines.
Conclusion

The immune system is a complex regulated system. An immune response generally develops under the influence of various control systems, which use negative feedback and mutual reinforcement mechanisms. The body operates on the basis of control system redundancy: the use of a surfeit of systems, which together determine the nature of the response. Redundancy prevents the complete breakdown of control and consequent response failure in the event of a problem affecting any one control system. By their effect on the Toll-like receptors, microorganisms influence system stability and probably also the balance between immunity, allergy and autoimmunity. However, much remains to be discovered about the way that the innate immune system works and is regulated.

3.3 Possible influence of vaccination on allergy

In the second half of the twentieth century, up to about 1990, the western world witnessed an increase in allergic and autoimmune conditions. Could this phenomenon be related to the introduction of large-scale vaccination? Is there any evidence to suggest that vaccination can interfere with maturation of the immune system? Such questions have arisen as insight into the working of the innate immune system has increased. In theory, vaccination could have either a positive or negative influence on allergy; it could make allergy more likely or protect against it. A summary of what is presently known about the relationships between certain vaccines and the prevalence of allergic conditions is presented below.

BCG

Some vaccines, such as BCG (Bacille Calmette-Guérin, a tuberculosis vaccine), the attenuated living vaccine against mumps, measles and rubella and the cellular whooping cough vaccine, trigger a predominantly Th1 response. It has been suggested that this group of vaccines may therefore protect against allergy to some extent. Other vaccines, such as the vaccines against diphtheria, tetanus and polio (DTP) and the acellular whooping cough vaccine, produce a mixed Th1-Th2 response. However, hereditary factors probably also play a role. Children who have a hereditary predisposition to allergic conditions may be less able to respond to vaccination in the anticipated way. Nevertheless, various studies have failed to find any evidence of an association between BCG vaccination and allergic conditions, regardless of the vaccination age.
MMR and measles vaccines

Researchers have also failed to find evidence of a link between allergy and MMR and measles vaccines. A prospective British study involving more than six thousand children found that both measles infection and measles vaccination could reduce the risk of hay fever, but only in children with older siblings. On the other hand a retrospective cross-sectional study in Denmark involving an non selected group of roughly ten thousand children between three and fifteen years old found that allergic skin conditions (atopic dermatitis) were more common among children who had received an MMR vaccination. This study found no association between measles infection or MMR vaccination and hay fever or asthma.

Shaheen et al performed a study in Guinea-Bissau, in which children who had acquired natural immunity to measles in an epidemic were compared with children who had been vaccinated. The vaccinated children were found to be more likely to suffer allergic conditions. Initially, it was supposed that a natural infection provided greater protection. However, another explanation for the difference between the two groups now seems more likely. During the measles epidemic, many children (25 per cent of those affected) died of malnutrition. The deaths may well have influenced the composition of the surviving population, insofar as the deceased were more likely to be children with lower levels of interferon-γ, a substance that protects both against measles and against allergy.

Cellular and acellular whooping cough vaccines

The research data concerning whooping cough vaccination and its possible influence on the development of allergic conditions are more difficult to interpret. Infection by the whooping cough bacterium, Bordetella pertussis, triggers certain T cells to produce large quantities of interferon-γ (IFN-γ), but little IL-5. It appears that Th1 cells play an important role in the acquisition of immunity to whooping cough. A similar response pattern is observed following the administration of a cellular whooping cough vaccine.

By contrast, the acellular vaccines nowadays used in most countries induce a mixed Th1-Th2 response, involving the production of not only IFN-γ and IL-2, but also IL-4 and IL-5. Furthermore, acellular booster vaccination triggers a predominantly Th2 response. In the event of either a natural infection or vaccination, considerable quantities of specific immunoglobulin-E (IgE) are produced. In animal experiments, the pertussis toxin, also found in the vaccines, has actu-
ally been used as an adjuvant to promote the production of IgE to defend against unrelated antigens. It has therefore been suggested that whooping cough vaccination might lead to sensitisation and the re-activation of allergic conditions. Some evidence to support this idea has been found, but other researchers have been unable to confirm the findings.

In a comparative study of infants’ immune response, Mascart et al observed a clear difference between the effects of cellular and acellular whooping cough vaccines. The acellular vaccines produced a clear Th2 response profile. However, it is not apparent whether this was a temporary phenomenon, or an outcome that actually predisposed the infants to clinically manifest allergies. The latter seems the less likely possibility, given that, in a follow-up study of children who had participated in a randomised study of various vaccine types, Nilsson et al found no differences in the development of allergic conditions.

Combination vaccines

Other researchers have similarly failed to find evidence that vaccination is a risk factor for allergy. A British study of 7098 hay fever sufferers and control subjects found no difference in the prevalence of hay fever within the various groups (those that had and had not received DTP, MMR or BCG vaccines).

In the prospective British research referred to earlier, McKeever et al investigated a possible association between vaccination with the DTP-polio or MMR combination vaccines and asthma or eczema. A link was found only among children who rarely or never visited the doctor. The authors suggested that this finding was due to those who had little contact with the medical profession being both less likely to have an existing allergy diagnosed and less likely to undergo vaccination. These circumstances, it was argued, would result in the misleading appearance of an association between vaccination and allergy.

Dutch researchers studying a reasonably homogenous group of eight-to-twelve-year-olds (n=1875) at strictly orthodox Christian primary schools similarly failed to find evidence of an association between vaccination against diphtheria, tetanus, whooping cough or Haemophilus influenzae type b infection and the development of asthma, hay fever, eczema or food allergy. Furthermore, Offit and Hackett and Koppen et al concluded from reviews of scientific literature that there were no published prospective or other epidemiological research findings to support the theory that vaccination could cause allergic or autoimmune conditions.
Conclusion

The Committee concludes that epidemiological research has so far produced no convincing evidence that vaccination can influence susceptibility to immunological conditions. Nevertheless, the currently available data do not allow the Committee to exclude the possibility of such an effect mechanism altogether. It is known that vaccines, particularly those designed to stimulate the production of antibodies in large numbers, can temporarily impair the quality of the response from the T lymphocyte system. However, it remains uncertain whether this can lead to increased long-term susceptibility to immunological conditions. Further research is required to clarify this matter.

3.4 Possible influence on maturation of the immune system

It is also pertinent to consider whether infectious disease plays a role in maturation of the immune system, and whether vaccination may interfere with this process. It has been suggested that reduced exposure to infectious disease in general, partly as a consequence of improved hygiene, may adversely affect the working of the immune system. This so-called hygiene hypothesis has received considerable attention both in the academic press and in the popular media. Vaccination could be significant in this context, insofar as it reduces the number of infectious diseases in circulation.

Since the discovery that the Toll-like receptors in dendritic cells (immune cells found in the skin and elsewhere) are specially adapted to the products of micro-organisms (microbe-associated molecular patterns, or MAMPs), it seems probable that micro-organisms play a role in development of the immune system. The function of the dendritic cells (DCs) is to ensure that antigens are presented to the T lymphocytes, thus initiating an immune response. When the Toll-like receptors are stimulated by MAMPs, the DCs produce various interleukins or other messenger proteins. These messenger proteins have an important regulatory effect on the immune system and therefore on the quality of the acquired immunity. Discovery of the Toll-like receptor system has brought the spotlight onto the role that micro-organisms play in regulating development of the immune system. This has in turn led scientists to consider how micro-organisms may influence the balance between immunity, allergy and autoimmunity.
Strachan’s original research

In 1989, Strachan published details of a study into the increasing number of reported hay fever cases. Strachan had studied data on more than 17,000 young British people born in March 1958, covering their first twenty-three years of life. It was found that hay fever was less common in large families, which the author suggested might be because children growing up in such families were exposed to more infectious disease. The hypothesis was that exposure in early life (or in the womb) afforded protection against hay fever.62

The position after ten years of follow-up research

Strachan’s study promoted a great deal of follow-up research. Ten years after his original publication, Strachan himself reviewed what by then was known.63 He concluded that the findings of research which had sought to attribute the rise of allergies and asthma to the decline in infectious disease had been unconvincing. Either no association had been found, or the apparent association had on closer examination proved not to exist or not to be causal.

However, the inverse association between family size and allergy prevalence had been confirmed by several other studies, including some that had utilised objective allergy data, such as the results of skin tests and specific immunoglobulin E tests. The association between family size and asthma was much less consistent, perhaps because the symptoms of asthma are only partially of allergic origin.

Researchers had, nevertheless, found a consistent association between the prevalence of objectively identified allergic conditions and socio-economical status. It also appeared that contact with domestic or farm animals had a protective effect. By contrast, the findings relating to contact outside the family (e.g. at nursery) were contradictory: some researchers had found that nursery attendance in early life was inversely associated with the prevalence of asthma or allergy, while others had found no such link.64-68

It had also emerged that there were significant, but poorly understood differences between East and West Europe in terms of the prevalence of allergic conditions. Various cross-sectional and prospective studies had found no consistent association between allergic conditions and either infectious disease in general or specific infectious diseases. Strachan therefore concluded that declining family size and rising socio-economic status could be no more than a small part of the explanation for the increased levels of asthma and allergy in the community.
Borchers et al also came to the conclusion that it was unclear why allergic conditions were gaining ground in the western world.

There is reason to believe that non-pathogenic exposure to micro-organisms may play a role in ensuring a balanced immune response. Of particular interest in this context are micro-organisms with which there would have been frequent contact in our evolutionary past, but to which modern humans are less exposed, such as worms, other parasites, some mycobacteria and certain gastrointestinal bacteria. By stimulating the Toll-like receptors referred to earlier, micro-organisms appear able to modulate dendritic cells and thus to attenuate immune activity. If exposure to certain micro-organisms under certain conditions does not lead to immunity but to attenuation or tolerance, interaction with such organisms could play a role in the development and regulation of the immune system.45,69

The microbial content of the gastrointestinal tract may also be influential. Bacterial colonisation of the gastrointestinal tract from the moment of birth leads to the immune system’s first and most substantial exposure to micro-organisms. Various studies have found a correlation between gastrointestinal flora and the development of allergic conditions. Drawing conclusions from the findings is not easy, however.

In a study of military cadets, Matricardi et al found that those with allergic conditions were less likely than non-allergics to have previously had *Helicobacter pylori*, *Toxoplasma gondii* or hepatitis A infections. No such correlation between infection history and allergic status existed where mumps, measles, rubella, chicken pox, cytomegalovirus or herpes simplex virus infections or respiratory infections were concerned.70 Other researchers have reported similar findings.71,72 It is unlikely, however, that the association between *Helicobacter pylori*, *Toxoplasma gondii* or hepatitis A infection and allergic conditions is causal.

In animal research both Sudo et al and Cebra et al found that gastrointestinal flora played a role in maturation of the immune system, particularly the development of immune tolerance of oral antigens.73,74 Given that considerable differences have been found between the composition of the gastrointestinal flora of children with allergic conditions and the flora of those without, it seems reasonable to suppose that micro-organisms may perform a similar function in people. In a study of two-year-old Swedish and Estonian children, Bjorkstén et al discovered that allergic children had fewer lactobacilli than non-allergic children.75 By monitoring Finnish children between the ages of three weeks and three months, Kalliomäki et al found that differences in gastrointestinal flora (fewer bifido bac-
teria and more clostridia) were precursors to the development of allergic predis-
position.\textsuperscript{76}

Conclusion

The Committee concludes that research into the hygiene hypothesis has yielded
no proof that the immune system can be compromised by insufficient exposure
to particular infectious diseases. On the other hand, there \textit{is} reason to believe that
infant gastrointestinal flora influences the development and regulation of the
immune system. Not enough is yet known, however, to say what the implications
of this are.

\section*{3.5 Starting age for vaccination}

Differences between children and adults

As explained above, there is no reason to believe that vaccination interferes with
maturation of the immune system. Nevertheless, it is pertinent to ask when the
immune system is ready for vaccination. In other words, from what age does va-
cination provide effective protection against disease?

At birth, both the cellular immune system and the body’s humoral immunity
(antibody production capability) are far from fully developed. Furthermore, neo-
nates retain antibodies derived from their mothers. In the event of vaccination
shortly after birth, therefore, some of the vaccine (antigen) might be suppressed
by these maternal antibodies before it is able to trigger a response from the
baby’s own immune system.

What is more, even though the developing immune system is able to respond
adequately to most vaccines, important differences still exist between a child’s
immune system and that of an adult.\textsuperscript{77,78} Much of the work done to compare
young and adult immune systems has necessarily taken the form of animal
research. However, the indications are that the differences observed in the con-
text of such research are, qualitatively speaking, shared by humans.

The general picture that emerges is that the infant immune system is not
g geared to the provision of prolonged protection. The levels of antibodies pro-
duced in response to vaccines administered only very early in life fall again rela-
tively quickly. By contrast, the vaccination of older children and adults usually
results in antibody levels that remain constant for a considerable time. The ability
to produce immunoglobulin type G antibodies increases gradually during
infancy. It is probable that this ability depends on the growing network of follic-
ular dendritic cells in the lymph glands. Furthermore, in children there is relatively little space available within the bone marrow for good plasma cell development. Finally, children produce fewer memory cells.

Nevertheless, the immune system is capable of responding adequately to vaccination, even in early childhood. This is apparent from research into various vaccines that are given to infants, which is summarised below.

Whooping cough vaccines

Belloni et al demonstrated that it is quite possible to vaccinate neonates against whooping cough. Although the antibody levels in most children were quite low following the first injection, they were much higher following the second injection than in children who had not been ‘primed’ as neonates. A study of mice found that vaccination shortly after birth was associated with low antibody levels, just as it is in people. Nevertheless, even these low levels were found to protect the animals against whooping cough.

Vaccines with polysaccharide antigens (such as Hib and pneumococci)

In principle, therefore, vaccines can be given even to very young infants. Vaccines consisting of polysaccharide antigens, such as the Hib and pneumococci vaccines, are an exception in this regard, however. In the first year or two of life, such vaccines produce very little response from the immune system. The B lymphocytes’ responsiveness to such antigens can be improved, however, by attaching the antigens to carrier proteins, so that T lymphocytes are called into action as well. Conjugated vaccines of this kind have been developed against infection by *Haemophilus influenzae* type b, meningococci C and pneumococci. These vaccines have now been used on infants and found to be very effective.

The studies conducted using such conjugated polysaccharide vaccines have been very instructive. Although the research is still in progress, and it is not yet clear whether the findings are equally valid in relation to all three conjugated vaccines, there appear to be a number of important similarities. Unlike ordinary polysaccharide vaccines (i.e. those that are not attached to proteins), conjugated vaccines are effective when administered to young children. Even when a conjugated vaccine is used, however, there is a threshold age, prior to which good-quality antibody production cannot be expected. This reflects the complex interaction between the innate immune system and specific acquired immunity.
Conjugated vaccines are probably able to engender prolonged resistance supported by immunological memory because they are able to use T helper cells to stimulate antibody response, thus leading to increased antibody functionality. This effect appears to be much greater in infants aged twelve months and above: the immune system apparently develops considerably in the period between four and twelve months.

These findings confirm that, generally speaking, it is not easy to achieve effective, lasting immunity by vaccination in the first year of life. Where vaccination is given early in the first year, a booster shot at about twelve months is necessary in most cases. Where initial vaccination takes place after the age of twelve months, a booster is not normally necessary.

The scope for single-dose vaccination is utilised in the Netherlands in the context of protection against meningococci C, where the vaccine is administered at the age of fourteen months. Where pneumococci are concerned, however, it is imprudent to wait so long before providing protection, since the disease burden is concentrated primarily in the first year of life. Vaccination against pneumococcal infection is therefore best started as early as possible, but a booster is then considered necessary in order to ensure lasting immunity.

Conclusion

The Committee concludes that vaccination immediately after birth is in principle quite possible. Nevertheless, for a number of reasons, the vaccination of neonates and very young infants is often less effective than the vaccination of older children. Where protection is sought against an illness that is liable to affect the very young, such as whooping cough and pneumococcal infections, the deferral of vaccination is not an option, however. When vaccination is provided early in life, more shots are necessary than when it is provided later. In many cases, booster vaccinations are also required.

3.6 The number of vaccinations

Is there a danger that providing numerous different vaccinations through the NIP might overload the immune system? No, probably not. The immune system is very good at coping with large numbers (many thousands) of antigens at the same time. Vaccination involves adding only marginally to the number of antigens to which people are exposed. Furthermore, production changes and other developments have in fact considerably reduced the number of different antigens in vaccines, especially the whooping cough vaccine. There is no evidence to sug-
gest that exposure to various antigens can overload the immune system or cause functional impairment in the long run.\textsuperscript{60}

It is possible, however, that vaccination may be less effective if certain vaccines are administered at the same time as others. Under such circumstances, the different immunological mechanisms associated with the vaccines influence one another. If, for example, several polysaccharide vaccines are conjugated on the same carrier protein, competition for receptors can occur. This will result in some antigens going unnoticed by the immune system, thus compromising the efficacy of vaccination. Overexposure to the carrier protein is also possible.

If the carrier protein used in a conjugated vaccine is itself used as a vaccine, as is the case with the tetanus toxoid and diphtheria toxin proteins, immunity to the illness associated with the protein itself may be positively or negatively influenced. The combination of vaccines therefore always has to be investigated experimentally.

### 3.7 Conclusion

Better understanding of the immune system opening the way for further development

The development of vaccinology into a science based on understanding of how the immune system works is an ongoing process. Various sophisticated techniques are available to the modern vaccine developer.

Ideally, a vaccine should contain only those proteins that will trigger exactly the right B cells, T helper cells and cytotoxic T cells and enable the acquisition of an adequate immunological memory. In many cases, however, not enough is known about the immune system for scientists to determine what components a vaccine should contain.

It appears that we can now produce an effective vaccine against any microorganism to which prolonged immunity can be acquired in the event of natural infection. It has so far proved much more difficult to develop vaccines against conditions to which only limited natural immunity can be acquired. However, significant advances have recently been made in understanding how the innate immune system works, thus paving the way for further development.

No evidence that vaccination has a negative effect

Parents and scientists have raised various important questions regarding immunological development during childhood. Could vaccination be responsible for
the increasing prevalence of allergic conditions seen in the second half of the twentieth century, up to about 1990? Is the immune system of a young child sufficiently well developed to respond properly to vaccination? Can vaccination interfere with normal maturation of the immune system? Is there a risk of overloading the immune system by giving too many vaccinations? The Committee has looked carefully at the scientific data and arrived at the following conclusions:

• There is no convincing evidence that the rise in allergic conditions has been caused by vaccination.
• Research into the hygiene hypothesis has yielded no evidence that the immune system can be compromised by lack of exposure to certain infectious diseases.
• The immune system is sufficiently well developed in early childhood to respond properly to vaccination.
• Important differences exist between the immune system of a child and that of an adult. The infant immune system does not appear to be geared to the provision of long-term protection. The ability to produce a lasting immune response increases significantly in the first six months of life.
• When vaccination is provided early in life, more shots are necessary than when it is provided later. Where vaccination is given early in the first year, a booster shot at about twelve months is necessary to provide lasting immunity in most cases. Where protection is sought against an illness that is liable to affect the very young, the deferral of vaccination is not an option, however.
• The immune system is very good at coping with large numbers (many thousands) of antigens at the same time. Vaccination involves adding only marginally to the number of antigens to which people are exposed. There is no evidence to suggest that exposure to various antigens can overload the immune system or cause prolonged functional impairment.
• It is possible, however, that vaccination may be less effective if certain vaccines are administered at the same time as others.
Chapter 4

Developments in the field of public information and communication

4.1 Increasing importance of good information provision

Low public profile of the target diseases

In the early decades of the NIP, the value of vaccination was obvious. Epidemics of the target diseases were still fresh in the public memory. Indeed, the polio epidemic of 1956 was the trigger for establishment of the programme. Measles, mumps and rubella were also familiar conditions until the introduction of universal vaccination in 1987; the public was aware of the illness, infirmity and death associated with them. Against this background, the need for public information was largely limited to practical advice.

However, the effectiveness of the NIP has been such that the target diseases now have a much lower public profile. As a result, people less readily appreciate the importance of the programme and sometimes question the need to participate. Having observed this development, the government has invested heavily in public information concerning the NIP in order that new generations of parents can be fully aware of the advantages and disadvantages of vaccination.

The Centre for Infectious Disease Control (CIb) also plays a key role in this field. In anticipation of the CIb’s creation, the Ministry of Health, Welfare and Sport (VWS) asked the RIVM in 2003 to improve communication with the pub-
lic and with clinic staff. In response, strategic communication plans were developed for the vaccination programme.

For the communication of information to the general public, there is now a website (www.rvp.nl) and an extensive series of leaflets on the NIP, the target diseases and the vaccines. The leaflets are available in sixteen languages. In addition, information is distributed at various public shows for expectant mothers and young families.

For people working at clinics there is a special e-mail newsletter RVP Nieuws (NIP News; see http://www.rivm.nl/rvp/actueel/nieuwsbrief/) and an information folder has been developed. The programme also has a printed journal entitled *Vaste Prik* (*Routine Jab*) aimed at this particular group.

**Public maturity**

The need to disseminate information is driven not only by the lower profile of the target diseases, but also by the increasing maturity of the general public. People are nowadays less inclined to accept what they are told by their government at face value and to act accordingly. People have easy independent access to the information required to form their own opinions.

Against this background, it is more important than ever that good information is placed in the public domain. There are two prerequisites for the existence of an effective public vaccination programme: the availability of good-quality vaccines and the willingness of parents to have their children vaccinated. Just as a great deal is invested in the quality and safety of vaccines to ensure that the first prerequisite is met, so investment has to be made in providing information to the general public and to clinic staff in order to ensure that the second prerequisite is met. However, little is known about what influences parents’ willingness to present their children for vaccination. If more were known, it would be possible to tailor public information accordingly and thus maximise its effectiveness.

At present, the Dutch public is very open to vaccination: more than 95 per cent of the children receive the full set of vaccinations. The Netherlands therefore comfortably meets the targets defined by the WHO.

In 2004 (before the RIVM’s current information was available), the NVI and twelve home care organisations conducted a study of public information concerning and acceptance of the old DTP-polio-Hib vaccine. Information was obtained from 1919 parents, who were asked to complete questionnaires and maintain journals. Child care nurses proved to be the primary source of information about NIP vaccinations: 78 per cent of the parents reported having received
Developments in the field of public information and communication

Information from the nurse. Some 80 per cent of the parents had already decided whether to have their children vaccinated; of the other 20 per cent, half said that the information provided by the clinic was a decisive influence. Only 10 per cent of the parents had used the Internet to obtain additional information. Fifty-six per cent of the parents indicated that the side-effects of vaccination were not as serious as they had imagined, 35 per cent said they were as expected and 9 per cent reported worse-than-anticipated side-effects (BAM van der Zeijst, personal written communication, 2007).

These findings are to some degree reassuring, but they also give rise to concern regarding the future. The main reason for concern is the slight drop in the infant vaccination rate witnessed in recent years. Furthermore, articles questioning the safety of the vaccines appear at intervals in the media, sometimes instigated by the Dutch Association for the Critical Use of Injections. Some parents, mainly from well-educated groups, are dubious about the merits of vaccination. Others, although disinclined to independent questioning, are easily put off by confusing or negative information.

Identifying the best ways of informing people about the effectiveness of vaccines and about any side-effects they may have is therefore extremely important.

4.2 Influences on inclination to accept vaccination

The first step is to establish what things parents take into consideration when deciding whether to have their children vaccinated. This is important because, to be effective, public information needs to address the matters in question.

4.2.1 Attitude, social influence and self-efficacy perceptions

Generally speaking, three factors influence a person’s inclination to do or not do something. The first is the person’s attitude, which is a product of his or her personal estimation of the advantages and disadvantages of a course of action, including the associated risks and the emotions it is likely to engender, such as anxiety, regret or relief. The second factor is social influence. The degree to which someone is swayed by social influences depends on how much they wish to meet the expectations of others, how much they seek to model their behaviour on that of others and how much social support they enjoy. The third factor is the person’s self-efficacy perceptions: whether the person believes he or she is capable of doing whatever it is that is being considered.

Attitudes, social influences and confidence in one’s capabilities are determined partly by background characteristics, such as knowledge and demographic
profile. Whether an intention is translated into action depends on the existence of practical barriers and actual capabilities. The various determinants of behaviour are illustrated in figure 5.

![Behavioural model](image)

*Figure 5* Behavioural model (an integration of the Theory of Planned Behaviour* and the Social Cognitive Theory*).

### 4.2.2 Dutch parents’ inclination to have their children vaccinated

So, what is known about the attitudes of, social influences on and self-efficacy perceptions of parents when it comes to having their children vaccinated? Little research has been done in this field in the Netherlands, but certain observations can nevertheless be made.

**Attitudes**

In general, Dutch parents have a positive attitude towards vaccination. A survey conducted by Paulussen et al (2000) found that less-educated parents and parents with families that included fewer than five children were the most likely to have a positive attitude. Their attitude to having their children vaccinated was apparently influenced by their estimation of:

- the infection risk;
- the reliability and safety of the vaccines;
- the regret they would feel if the child were not vaccinated and subsequently succumbed to the disease.

Attitudes were influenced to a much lesser extent by knowledge of the diseases and vaccines, familiarity with children who had previously suffered the target illnesses, and the possibility of ‘freeriding (taking advantage of the protection afforded by living in a vaccinated population, without having one’s own child vaccinated). One important point to come out of the survey was that, among par-
ents who were unsure whether they had done the right thing, uncertainty often stemmed from their estimation of the credibility of the information sources. It was apparently assumed that care practitioners deliberately overstated the advantages of vaccination and belittled the disadvantages. They were also doubtful as to whether care practitioners were in fact fully conversant with the potential risks associated with vaccination.89

Ethnic-minority parents were predominantly positive about having their children vaccinated. This finding was consistent with the work done by Hardon et al (1998) in Arnhem and Amsterdam. Almost no aversion on religious grounds was encountered.89 A study undertaken by Timmermans et al (2005) at about the time that meningococcal C vaccination was introduced confirmed that the ethnic minorities in the Netherlands were almost universally positive about vaccination, although they tended to be less well informed and to have encountered less public information about the NIP than the ethnic majority. Ethnic majority parents were more circumspect, although in the vast majority of cases this did not lead to aversion. Critical attitudes were most common among well-educated parents.91

Conclusions about parental attitudes can also be drawn from the reasons why people miss vaccinations. The 2000 study performed by Paulussen et al found that people with large families, churchgoers and people from the eastern, northern and southern regions of the Netherlands were more likely to miss vaccinations. The reasons given by parents for not completing a course of vaccinations were as follows: unable to recall the reason (24 per cent), risks associated with vaccination (10 per cent), religious convictions (6 per cent), no appointment received (6 per cent), missed vaccinations to be given shortly anyway (3 per cent), and moral convictions (2 per cent). In other words, non-attendance can sometimes be attributable to attitude and sometimes to practical obstacles. People tend to be slightly less positive about participation in the NIP before they have children than once they start a family.89

Thus far, we have considered attitudes to existing vaccinations. However, parents’ views on possible extensions to the programme are also important. In 2005, Hak et al investigated parents’ willingness to have their children vaccinated between the ages of three months and five years by asking them to comment on a hypothetical situation: the addition of five new vaccines to the existing NIP, to provide protection against influenza, hepatitis B, tuberculosis, smallpox and SARS. Forty-six per cent of respondents were positive about introduction of the five vaccines, while 11 per cent were opposed to them all. People were more positive about new vaccinations whose introduction was justified on public health grounds. Only a quarter of respondents were in favour of introducing vac-
cinations primarily for reasons of cost. Parents’ attitudes were also shaped by the anticipated discomfort for the child: if the inclusion of new vaccines were to mean that three or four injections would be needed in a single session, three quarters of the parents would not be in favour.92

The research by Paulussen et al also found evidence that there is much less support for new vaccinations than for those already provided. More educated parents are particularly likely to question further expansion of the NIP. Generally speaking, the best-supported of the proposed additions was vaccination against meningococci; far fewer people were in favour of vaccination against chicken pox.89

How firmly established are the attitudes described above? It seems that most parents make little or no assessment of the potential advantages and disadvantages before deciding whether to have their children vaccinated. This could spell problems for the rate of vaccination in the future, since positive attitudes that are not based on the active consideration of information are liable to alter in the face of counterarguments.93 The reason being that, if parents are presented with new information about the (supposed) risks associated with vaccination, they have no verified arguments to fall back on. This can lead to uncertainty about the wisdom of an earlier decision or intended course of action. Under such circumstances, parents may simply ignore the new information; or they may refer back to sources of information that they trust (which, the research suggests, do not necessarily include the staff at their local clinic).

Social influences

There is no research evidence that social influences have a significant bearing on parents’ inclination to have their children vaccinated. Attitudes and self-efficacy perceptions appear to be the primary predictors of behaviour in this sphere.

Self-efficacy perceptions

The self-efficacy perceptions that influence Dutch parents’ inclination to have their children vaccinated predominantly concern the ability to:
• resolve any practical problems they may encounter; or
• protect the child against disease without vaccination.
Barriers

The studies carried out in the Netherlands all indicate that the vast majority of parents intend to have their children vaccinated through the NIP. Most make good this intention. Some, however, fail to do so because of circumstances that they encounter.

Paulussen et al found that (perceived) practical difficulties sometimes played a role in people missing vaccinations. Six per cent of non-attenders indicated that they had never been asked to come to the clinic for the missed vaccination.

The work done with ethnic minority parents by Hardon et al (1998) indicated that vaccinations were missed mainly because of practical difficulties: not daring to respond to the invitation because of irregularities in residency status, the parents or child being ill, the family being away on holiday, the parents being unable to get away from work, and so on.90

4.2.3 The inclination of parents in other countries to have their children vaccinated

As in the Netherlands, researchers in other countries have devoted little attention to the factors that influence parents’ inclination to have their children vaccinated. Furthermore, the findings of the research that has been done are not necessarily valid in relation to the Netherlands, since different countries have different vaccination regimes and cultural differences can play a role as well. Nevertheless, a number of findings are worthy of note.

What makes parents averse to having their children vaccinated? The studies conducted outside the Netherlands have identified a number of relevant attitude factors:

- Parents are not convinced that certain vaccines are necessary or effective.94
- Parents are worried about the possibility of adverse reactions or imagine that adverse reactions are common.95
- Parents believe that the risks associated with non-vaccination are not particularly great.96
- Parents perceive the benefits of vaccination to be minor.95
- Parents believe that getting ill is more natural than vaccination.95,97
- The child is or has recently been ill.98

The influence of socio-demographic factors on attitude is not straightforward. One consistent finding is that children in large families are less likely to be vaccinated than children in small families. Religious beliefs appear to be significant
primarily in the Netherlands. They are not normally taken into account by most non-Dutch researchers and barely mentioned in non-Dutch research literature.

Generally speaking, the second determinant of behaviour – social influence – is not particularly important in relation to participation in vaccination programmes. Social influences do have an indirect bearing on parents’ inclination to have their children vaccinated, however. There tends to be an implicit sense that everyone else does it, so it must be OK. Various authors also highlight the importance of the attitude of the care practitioner in his/her role as a key figure in the parents’ social environment. The advice of a GP, paediatrician or nurse can deter parents from having a child vaccinated.95 On the other hand, a practitioner with a positive and active attitude can encourage parents to go ahead with vaccination. It is therefore very important that practitioners are themselves well informed; even among professionals, misconceptions regarding the risks associated with vaccination can persist.94,97

Only one non-Dutch research group working in this field – Meszaros et al (1996) – have taken account of self-efficacy perceptions. This team found that the less confident parents were in their ability to protect their children from infection and its consequences, the more inclined they were to have their children vaccinated.96

The international scientific literature also identifies a number of practical barriers. Vaccinations are often missed, apparently, because of the child being ill.97,98 Other difficulties include the accessibility of the care establishment and the waiting time. A commonly-cited problem is lack of follow-up in the event of a missed appointment.94 These barriers probably do not exist in the Netherlands.

4.2.4 Conclusion

The vast majority of parents in the Netherlands are inclined to have their children vaccinated. For many, there is no question of not doing so. However, there is reason to believe that parental attitudes are not in all cases firmly established or based on information that has been consciously registered. Under such circumstances, there is a danger that attitudes can be changed by biased or negative information, and that parents can be led to doubt the wisdom of decisions they have previously made or intentions they have formed.

Care practitioners are influential figures in parents’ social environment. As such, they can make parents more or less inclined to have children vaccinated. Furthermore, practical difficulties play a role in turning intention into action. Nearly all parents want their children vaccinated, but some are put off by obstacles that they encounter.
What are the implications of these observations for the provision of information regarding the NIP? In the years ahead, parents should be encouraged to actively consider the information made available to them – to make a conscious assessment of the advantages and disadvantages of vaccination, on the basis of reliable and accessible information. This will hopefully reinforce their attitudes and ensure that they are less easily swayed by new or contradictory information. Various ways of achieving this aim are set out on the following pages.

4.3 Public information initiatives

What can be done in the public information sphere to ensure that parents have confidence in the effectiveness and safety of the NIP, and therefore have their children vaccinated? How can they be encouraged to actively assess the information available to them?

4.3.1 Importance of a systematic public information programme

Public information initiatives should always take place in the context of a programme of activities designed to promote a particular form of behaviour. The provision of information is not on its own sufficient, because so many factors play a role in the formation of intentions and the translation of intentions into action. The use of public information as a policy tool also requires a systematic approach based on scientific principles (see also the Health Council’s report on mass-media public information activities, Plan de campagne [Plan of Campaign]99).

In practice, there is no such systematic approach. Many public information initiatives may be described as input driven. Such initiatives tend to work on the principle, as indeed the NIP does, that people are rational beings who will act in the way that is to their greatest advantage (e.g. in the interest of better long-term health). In many cases, however, this approach is not effective. Most hardened smokers, for instance, know just as well as non-smokers that smoking is unhealthy. However, such people perceive there to be a short-term benefit that they value more greatly than their long-term health. To be successful, communication needs to focus on the way that a piece of advice or a product will be received by the user, and the value he or she will attach to it.

Effective public information is designed with the target group firmly in mind. The various phases of the design process are considered below, with the emphasis on identifying the factors that need to be taken into account in each phase in
order to realise the objective of ensuring that parents’ inclination to have their children vaccinated is maintained and where necessary reinforced.

4.3.2 Influencing attitudes

The first way of influencing the determinants of behaviour, and thus the behaviour itself, is to change attitudes. This involves providing people with information that will change their view of the advantages and disadvantages of a given course of action. This end can be achieved by the following:

- Correcting possibly erroneous assumptions about the consequences of a course of action (e.g. letting people know that vaccination does not increase the risk of cot death).
- Confirming existing assumptions (e.g. making sure that people know that unvaccinated children can still be infected, even if the children around them are vaccinated).
- Providing information about advantages and disadvantages that people in the target group are not generally aware of (e.g. making it clear that the meningococcal vaccine only reduces the risk of meningitis; it doesn’t remove it).
- Influencing the value that people in the target group attach to certain advantages and/or disadvantages.

Intervention of the kinds described above necessarily entails setting out the risks, presenting arguments in a way that takes account of the target audience’s degree of involvement and being sensitive to the emotional aspects of the decision-making process.

1 Communicating information about risk

Knowledge is a precondition for behavioural change, but no guarantee of such change. There have been many occasions in the past when the communication of factual information about health risks has failed to have the desired effect on the target audience.

This should not in fact be surprising, because communicating information about risk can be very difficult. Anyone who wishes to influence a target group’s assessment of the advantages and disadvantages of a form of behaviour by imparting information needs to be well aware of the pitfalls. The general public often takes a different view of risk from that taken by experts.

What matters most to ordinary people is not whether their assessment of risk is objectively correct, but whether it is useful as a means of enabling them to
make better decisions and function better in a world where so much is uncertain. Consequently, it is usually better to provide information about the implications of developing a particular health problem than to tell people about the numeric risk of developing it.¹⁰⁰

The general public does not weigh up risk according to statistical principles, but in most cases using simple, accessible rules of thumb, or heuristics. A GP, for example, is liable to remember the one child that suffered a rare adverse reaction to vaccination much more vividly than the many children who were unaffected. As a result, he or she will ‘feel’ that the risk of such a reaction is higher than it actually is.

On the other hand, unrealistic optimism is also problematic.¹⁰¹ Many people believe that they are at less risk than most of suffering misfortune, e.g. developing a disease. They are also inclined to imagine, mistakenly, that they are alone in having taken precautions. Public information material can explicitly address this kind of misconception.

It also seems that it is important how information about risk is presented; in psychological literature, this is referred to as ‘message framing’. People are more inclined to do something if told about the chances of them benefiting than if told about the chances of suffering adverse consequences if they don’t do it. For example, patients are more likely to opt for a given therapy if told that there is a 90 per cent chance of survival than if told that there is a 10 per cent chance they will die. The results of the experiments conducted by Rothman et al suggest that the same principle applies in relation to behavioural advice about the avoidance of risk, such as advice on stopping smoking.¹⁰⁰

The implication of this is that public information aimed at parents who perceive vaccination as a form of risk avoidance should focus on the advantages, both in the long term (‘Vaccination reduces the chance of your child suffering a serious infectious disease’) and in the short term (‘You can rest easy once your child has been vaccinated against these dangerous diseases’). However, parents who are inclined to see vaccination itself as the risk, i.e. something that could bring disadvantage – because, for example, they place a lot of emphasis on the possibility of adverse reactions – the opposite line should be taken. In other words, the focus should be on the chances of being disadvantaged (‘If an unvaccinated child gets the illness in question, there is little/less chance of effective treatment’).

Another consideration is that people are more ready to accept a small chance of serious disadvantage than the certainty of modest disadvantage, such as the temporary concern some people experience as a result of participating in a
screening or vaccination programme. Furthermore, they will opt for the certainty of a small benefit, ahead of a small chance of a substantial benefit. Hence, a message such as ‘You will feel reassured once your child has been vaccinated against these dangerous diseases’ has more appeal than ‘Vaccination reduces the risk of your child suffering a serious infectious disease’.

Finally, it is known that people tend to underestimate the risks associated with activities over which they have control, such as smoking. By contrast, they overestimate the danger posed by things outside their control, such as modified food. The (perceived) risk of an adverse reaction to vaccination comes under the second category. This explains the popular disquiet generated by the meningococci epidemic of 2001, which involved a potentially serious infection that was communicated from person to person unnoticed, in the context of everyday contact.

2 Taking account of differences in involvement

Naturally, the success of any attempt to change attitudes depends on the strength of the arguments one brings to bear. This implies that the points made must be plausible, relevant in the eyes of the audience, and preferably new.

Strong arguments are important primarily in situations where one’s target audience is very involved with the subject matter, as with parents looking to make an informed decision about participation in the NIP. Under such circumstances, people are more motivated to actively take in the information presented to them. Any flaws in the arguments put forward to such an audience will soon be found out. Acceptance of a message by people who feel less involved with an issue depends not so much on the quality of the arguments, as on whether they are consistent with what other people think or whether they come from a credible source. Consequently, if a trusted source presents a weak argument, it is likely to be accepted anyway if the audience has little incentive to actively assess what they are being told.

Generally speaking, a source that communicates information about risk will be regarded as reliable if perceived to possess expertise and not to have a vested interest in the subject. It cannot therefore be assumed that the government will be regarded as a reliable source of information concerning the risks associated with the NIP.

In particular situations, people are apparently more receptive to information from certain sources. When considering views based on verifiable facts or when concerned that their own views may be based on misconceptions, they more
readily trust information from unequivocal sources. In situations where people are surer of themselves, they are more inclined to accept information selectively, admitting only that which supports their established thinking. This too needs to be taken into account when addressing particular target groups.

3 Taking account of feelings

Attitude is based not only on cognition, but also on emotion. Public information activities can take account of this fact by, for example, drawing attention to ‘anticipated regret’. This involves asking people to imagine the regret and remorse they will feel if in due course they are confronted with the adverse consequences of their present behaviour.

It is also possible to anticipate the audience’s anxieties. Historically, this has been a common tactic in public information campaigns, which have sought to use shocking examples to persuade people to change their behaviour. However, such tactics are by no means always successful. The reason being that the reinforcement of anxiety can elicit two types of response: 1) the information recipient seeks to manage his/her anxiety, e.g. by denying the risk of infection or the effectiveness of the vaccine, or 2) the information recipient seeks to manage the risk that underpins the anxiety, e.g. by opting for vaccination. Only one of these two responses leads to the behavioural modification sought by the campaigner.

Anxiety-inducing public information therefore needs to be carefully designed to induce the desired form of risk-management response. Such a response is more likely if the information recipient considers the promoted form of behaviour both practicable and likely to be effective. Otherwise, anxiety-inducing public information is liable to be counterproductive, as the audience opts for an anxiety-management response and may refuse to consider new information on the same subject for fear of bringing on further anxiety. The audience can even become unwilling to consider any information from the source in question, on the basis that such information is liable to be something the recipient would rather not know. In other words, anxiety inducement is an effective tactic only if it is clear is that the audience will feel able to opt for risk control. Provided that this is the case, the tactic can serve as a useful driver of attitude or behavioural change.

Another way of persuading people to change their attitudes is to help them evaluate their behaviour by reference to personal standards and values. This approach can be useful as a means of highlighting inconsistencies. Someone who considers responsible parenting to be very important may, for example, be per-
suaded that not having his/her child vaccinated is inconsistent with his/her own values.

So far, we have mainly considered ways of changing negative attitudes. Where the NIP is concerned, however, it is at least equally important to reinforce existing positive attitudes. There are various ways of doing this within the public information sphere. One is to administer a ‘psychological vaccine’ seeking to make people resistant to possible attacks upon their existing positive attitude or habit. The key elements of psychological vaccination are: 1) warning people that attempts will be made to change their attitude, and 2) providing people with the information needed to refute negative assertions.

4.3.3 Seeking to shape social influences

People often base their perceptions of reality on the reactions and behaviour of others. Particularly when unsure of themselves, people are likely to compare their views with those of others. Under other circumstances, too, people are apt to try and conform to others’ expectations, for fear of isolation. Public information can be geared to these tendencies in a number of ways:

• By illustrating that (many) other people behave in the desired manner
• By illustrating that the desired form of behaviour is socially advantageous
• By providing people with the skills necessary to resist negative social pressure
• By mobilising social support to help people resist negative social pressure or pursue the desired course of action

Modelling is important as a means of harnessing the power of social influence and thus teaching skills (including the skills needed to resist social pressure). Various forms of modelling may be used in the public information sphere. One is recounting the experiences of people who serve as role models.

4.3.4 Reinforcing self-efficacy perceptions

People are disinclined to try to do things that they believe are beyond their capabilities. A person’s belief that he or she can or cannot do something in the future is based mainly on previous experience of similar activities.

Where vaccination is concerned, this is relevant mainly in relation to communication with care practitioners. If, for example, someone has previously tried unsuccessfully to discuss concerns regarding the safety of a vaccine with a care
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practitioner, he or she will be reluctant to attempt the same thing again. If this reluctance becomes firmly established, the person is likely to turn to other, potentially less desirable, sources of information. Public information can anticipate such problems by, for instance, preparing people for such experiences by making them aware of other reliable information sources.

4.4 Conclusion

Good information provision is increasingly important

In recent years, various media and channels (leaflets, website, outreach activities) have been used to provide the public with information about the NIP. The Committee considers such initiatives very important. The established activities have helped the programme achieve – and thus far sustain – a high vaccination rate. However, new forms of information provision will in due course probably be needed if that high vaccination rate is to be maintained in the longer term.

There are two reasons for this. First, there is the effectiveness of the NIP itself. The target diseases are gradually receding from public consciousness, creating a danger that the programme may become a victim of its own success. Second, the public is increasingly mature, and the inclination to think and act independently is only likely to increase in the future.

A stronger scientific basis is needed to support information provision activities

Unfortunately, it is not possible to draw up a blueprint for the provision of public information about the NIP in the scenario sketched above. The Committee believes that, if the NIP is to remain effective, it is very important to reinforce the scientific basis of communication and public information activities. To this end, the committee makes the recommendations set out below.

1. Research should be conducted into parents’ inclination to have their children vaccinated

No more than the first tentative steps have been taken – in the Netherlands or elsewhere – towards determining the factors that influence parents’ willingness to have their children vaccinated. Furthermore, not enough is known about the differences between relevant subgroups. The Committee therefore wishes to see research undertaken into these matters. It is recommended that data on parents’
The future of the National Immunisation Programme: towards a programme for all age groups

inclusion to have their children vaccinated be linked to objective data on the actual vaccination status of the surveyed parents’ children, rather than to the vaccination status as reported by the parents. Once a system is in place for monitoring the vaccination status of children and their parents’ openness to vaccination, it will be possible to determine the impact of future changes to the range of vaccinations available, and to adapt the public information strategy accordingly.

2 Encourage parents to actively assess information

On the basis of what is known about the background to parents’ inclination to have their children vaccinated, the Committee recommends that public information about the NIP be designed to encourage parents to actively assess the information available to them concerning the advantages and disadvantages of vaccination. Promoting the active assessment of information about both the benefits and the possible drawbacks may be expected to increase the public’s ability to be objective when confronted with arguments against vaccination. This implies talking openly about any adverse reactions and about other topics that can cause parents unease. Otherwise, there is a real danger that parents will lack the knowledge required for an appropriate response. If left in doubt, they are liable to turn to other – not necessarily balanced – sources of information.

Given these circumstances, it is important that child health practitioners are perceived as reliable sources of information. Incomplete or exclusively positive public information is unhelpful, since it undermines perceptive recipients’ faith in the credibility of the source. It is worth noting that, when this topic is discussed in the media, the proponents of vaccination are typically reticent to speak out. As a result, the opponents of the NIP presently seem to monopolise the public debate on the risks (supposedly) associated with vaccination.

3 Implement public information strategies systematically

The information about the NIP provided to parents should in the future be developed systematically. That implies first gaining an understanding of the knowledge, beliefs and emotions that underpin parents’ willingness to have their children vaccinated. Insight into the attitudes of, social influences upon and self-efficacy perceptions among members of the target group is also essential. It is only with such understanding and insight that theoretical knowledge and methodological skill can be utilised effectively to influence behaviour.
Research previously undertaken in the Netherlands and other countries has produced evidence that the determinants of parental vaccination behaviour are not uniform across the population. We know, for example, that doubts concerning the value and safety of the NIP are most common among well-educated parents. Furthermore, information needs differ from one subgroup to another. Going forward, there is a need for research into the validity of universal public information for all parents. Modern media, such as the Internet, are ideal for tailoring public information to suit the audience. At present, however, not enough is known about the determinants of parental vaccination behaviour to allow for the targeting of information on particular groups.

4 Test public information material

Before public information activities are implemented, the materials should undergo carefully designed experimental pre-tests. Given the NIP’s importance for public health, every effort must be made to avoid counterproductive information activities. To this end, alternative messages should be tested on small groups of parents (e.g. in a laboratory setting) to determine what intended and unintended effects they have. Particular care should be taken when considering how to present information about matters such as the chances of certain benefits and drawbacks being realised.

5 Professionalise the communication of information to the public by care practitioners

The Committee believes it is important to invest in further professionalisation of child health practitioners’ activities in the field of interpersonal information communication. Such practitioners occupy a strategic position, as the only professionals in direct contact with parents. Furthermore, personally communicated information usually carries more weight than public information communicated via the mass media. The reason being that, in a person-to-person setting, information can be adapted to suit the individual parent. Various studies, mainly conducted in other countries, have suggested that the attitude of care practitioners has a major bearing on parents’ inclination to have their children vaccinated.

However, very little is known about Dutch care practitioners’ personal views regarding the effectiveness or safety of vaccination, or about the influence that practitioners’ views have on parents. Nevertheless, there is reason to believe that not all practitioners have the conversational and communication skills apparently
needed to provide parents with appropriate information. The skills in question are complex, and have to date largely been ignored in the context of professional training.
Part II

Context
The future of the National Immunisation Programme: towards a programme for all age groups
Objectives

5.1 Primary objective of the NIP

The National Immunisation Programme is constantly developing. That much will have become clear from the first part of this report, in which the history of the programme was outlined and what is currently known about immunology and public information was considered. Against this background, it is important to ask what the programme’s present objective is.

With the possibilities for vaccination increasing all the time, the objectives of the national programme need to be clearly defined and properly supported. The Committee believes that the general objective of the NIP should be as follows:

To protect the people and society of the Netherlands against serious infectious disease by means of vaccination.

The provision of such protection is, in the Committee’s view, a natural task for government. The government has a responsibility to protect the public in situations where there is a substantial threat to health, and individuals (or their parents) would find it difficult to protect themselves.

The situation with regard to vaccination fulfils those criteria. Vaccination is the most effective way of protecting against many infectious diseases. In most cases, protection is afforded not only to the vaccine recipient, but also to wider
society, since circulation of the bacterium or virus in question is inhibited. Thus, the national programme also benefits unvaccinated people and people who do not respond adequately to vaccination. Hence, the prevention of communication contributes significantly to public health.

However, the importance of the NIP extends beyond the public health sphere. If there is a realistic possibility that contact with other people will involve exposure to and communication of serious disease, that possibility and the associated disquiet is liable to lead to social problems. Government involvement is therefore essential.

That is not to say that the Committee believes everything is controllable. It would be foolish to imagine that infectious disease can be eradicated altogether. There will always be conditions for which no vaccine is available. Furthermore, there will inevitably be vaccinations that are of benefit primarily to the individual, rather than the wider community, and do not therefore have a place in the national programme.

5.2 Three strategies

In support of the primary objective of protecting the people and society of the Netherlands by vaccination, three secondary objectives may be identified:

1. To eradicate certain infectious diseases
2. To create and maintain herd immunity
3. To protect as many individuals as possible

The eradication of certain infectious diseases

Coordinated international action has succeeded in eradicating the dangerous disease of smallpox. The World Health Organisation (WHO) has identified polio, measles and congenital rubella syndrome as candidates for elimination.*

Attainment of this goal in the next five to ten years appears to be most realistic in the case of polio. Large parts of the world are already polio-free. Under such circumstances, eradication is feasible, since there is no animal reservoir of the polio virus. Whether the polio virus will actually be eradicated is another matter, however. Major obstacles exist, in the form of lack of political will, the

* Elimination is the exclusion of a disease from a defined region. Following elimination, there remains a risk of reintroduction from another region. Eradication is the total exclusion of the relevant pathogen from the environment, so that it cannot return.
cost of the necessary action and the fact that the great majority of most infections are asymptomatic.

It is also uncertain which vaccine should be used. The injectable inactivated vaccine (IPV) normally used in the Netherlands is very expensive for global use. The cheaper and more commonly used living attenuated vaccine (OPV) multiplies in the gut of vaccine recipients. This can be helpful, since it enables communication of the virus to others, who are thus themselves immunised. However, it also means that the vaccine virus can recombine with other enteroviruses and thus become more virulent. The WHO’s existing strategy for the eradication of polio involves all countries ceasing to use OPV in due course. Thereafter, any nation that wishes to continue providing polio vaccination will need to switch to using IPV.

Another problem exists, in the form of people who continue to excrete virus for a long time following natural infection. Furthermore, it is not at all clear how long vaccination should continue following the last reported case of polio.108,109

Where it is possible, the eradication of an infectious disease is indeed the most effective way of relieving the associated disease burden and thus protecting people and society. In many cases, however, the second goal (achieving and maintaining herd immunity) will be the best viable form of protection, or the most desirable.

The creation and maintenance of herd immunity

In situations where eradication is not a realistic aim, the scope for creating herd immunity should be explored. Herd immunity is a phenomenon that enables people who have not acquired immunity through natural infection or vaccination to nevertheless enjoy a degree of protection, on account of living among other people who are immune. In other words, herd immunity reinforces the effect of vaccination, resulting in a greater overall effect than might be expected purely from the number of vaccinated people in a population.

Indeed, if a vaccination provides prolonged or lifelong resistance, the related condition may be eliminated without absolutely everyone being vaccinated. Where mumps, measles and rubella are concerned, for example, a vaccination rate of between 90 and 95 per cent is sufficient to prevent the disease spreading. Efforts to establish herd immunity are entirely consistent with the public nature of the NIP.
The protection of as many individuals as possible

If it is clear that herd immunity is an unobtainable goal – because, for example, vaccination take-up is low, or there are serious implementation difficulties – the third subordinate objective may be adopted: to protect as many individuals as possible.

5.3 Selection of target groups

Children

The NIP was originally set up to tackle childhood diseases. For sound practical reasons, the programme continues to focus primarily on the vaccination of children. For equally sound reasons, the way that the NIP is organised justifies making extra effort to prevent disease among children, as the principal vaccine recipients. It is important that parents can rely on the programme. Therefore, it is undesirable to have a situation such as that involving whooping cough, which can occur (with serious consequences) before effective vaccination is possible (in the first months of life) or in children who have been vaccinated not many years previously. The avoidance of such situations sometimes warrants special attention.

Neonates

Neonates form another important target group, because their immature immune systems are particularly vulnerable.

Belloni et al have demonstrated that, in principle, it is possible to vaccinate children against whooping cough immediately after birth.81 This option needs to be compared with alternative means of protecting very young infants. One such being the vaccination of older children and adults in direct contact with neonates (cocooning). In the Netherlands, children born to hepatitis B carriers are now given their hepatitis B vaccination as soon as possible after birth.

In other parts of the world, neonatal vaccination (against conditions such as hepatitis B and tuberculosis (BCG)) is more normal. However, the Committee is cautious about the vaccination of neonates, for two reasons. First, the possibility cannot be excluded that some vaccinations have a temporary or lasting adverse effect on development of the immune system. Furthermore, the presence of maternal antibodies may limit the scope for effective vaccination in the period
immediately following birth. Second, it is considered generally desirable to avoid unnecessary medical interventions in the first two months of life.

**Adolescents**

Adolescents are increasingly seen as a target group for vaccination because of the availability of vaccines against, for example, hepatitis B and human papilloma virus (HPV; an important precursor of cervical cancer). Both infections are sexually transmissible. In due course, vaccines may well become available against herpes simplex virus type 2 (HSV-2), *Chlamydia trachomatis*, gonorrhoea and HIV. Communication of these infections could be prevented by vaccinating people in early adolescence (around the age of eleven or twelve). This would, however, entail building additional treatment junctures into the vaccination scheme.

**Adults**

It is no longer assumed that the programme will remain limited to the vaccination of children. In cases where vaccination does not afford lifelong immunity (protection), it is pertinent to ask whether a public programme such as the NIP should not also seek to protect adults. To answer that question, it is necessary to be clear about what one wishes to achieve. Many NIP target diseases are dangerous primarily to young children, so the maintenance of immunity within the general population is not justified on adult health grounds. However, if adults constitute a source of infection for vulnerable children – as with rubella and whooping cough – the vaccination of certain groups may be justified on child health grounds.

**Pregnant women**

Within the adult population, pregnant women should form a special potential target group for programmatic vaccination. The reason being that, by vaccinating such women, it may be possible to enhance the protection enjoyed by their children from birth.

In the first months of life, a child enjoys natural passive protection provided by antibodies from its mother. This protection remains important in the period before the child has acquired immunity, either as a result of vaccination or natural infection. In other words, nature has provided neonates with a degree of protection, but this is not always sufficient.
It is therefore appropriate to consider whether the temporary protection afforded by maternal antibodies can be reinforced by vaccinating the mother before or during pregnancy. Maternal antibodies are not always advantageous, however: in some cases, they neutralise vaccines and thus impair the acquisition of immunity. Consequently, some vaccinations are most effective once maternal antibody levels have fallen somewhat.

It is important to bear in mind that, during pregnancy, an immunological situation prevails which is quite unlike the situation for which vaccines have been developed. This does not, however, preclude the vaccine of pregnant women. Studies have been conducted which indicate that whooping cough vaccination during pregnancy is both safe and effective (the whooping cough vaccine is not a living vaccine).

In principle, therefore, the vaccination of expectant mothers is a viable method of promoting the transfer of protective antibodies. Nevertheless, the Committee does not generally favour the provision of vaccination during pregnancy in the context of public vaccination programmes. There is a danger of congenital abnormalities or health problems being lightly attributed to maternal vaccination, with potentially serious implications for essential public confidence in the NIP. Moreover, the Committee is opposed to the vaccination of pregnant women using attenuated living vaccines, such as the existing vaccine against measles and a vaccine against respiratory syncytial virus that is under development.

Women who are planning a family

Another special group of adults for whom vaccination might be considered is women who are planning a family. The Committee believes that the scope for and limitations of vaccination in the context of preconception advice should be investigated. Another Health Council committee is currently looking into the possibility of bundling the provision of health advice, screening and treatment for women who are planning a family. Vaccination under such circumstances might be desirable as a means of protecting the unconceived child against whooping cough, rubella and measles – and possibly in due course against RSV infection.

Where whooping cough is concerned, preconception consultation could be used as an opportunity to identify the adults who will have direct contact with the child, and should therefore be considered for vaccination.
Where rubella and measles are concerned, it could be helpful to establish the extent to which women who have probably not been vaccinated through the NIP possess protective antibodies. Some infectious diseases cannot continue in circulation if the effective immunisation level is above a critical threshold; for mumps, measles and rubella, the threshold is at about 90 to 95 per cent of the population. With such diseases, immunity against a given strain of the causal virus is persistent and can even be lifelong. As a result, it is possible to eliminate or even eradicate mumps, measles and rubella. If, however, elimination is not achieved, and epidemic outbreaks continue to occur from time to time, universal vaccination can lead to a situation where the level of immunity in the population actually falls because of the micro-organism’s reduced circulation. Women who reach adulthood in such an environment tend to have few of the relevant antibodies and therefore pass less protection on to their children.

During the epidemics of measles and rubella in vaccination-averse communities in 1999-2000 and 2004-2005 (respectively), no cases of either illness were reported in women who had previously been vaccinated, or in such women’s newborn babies. Apparently, immunity acquired through natural infection or vaccination is persistent or even lifelong. Consideration should therefore be given to providing preconception vaccination for women who have (probably) never been vaccinated against rubella or measles and who carry few antibodies. The population-level effectiveness of providing vaccination in connection with preconception advice would need to be compared with that of providing vaccination to children using alternative immunisation schedules.

The possibility of introducing vaccination for women who are planning to start a family begs an important question: how high do a prospective mother’s antibody levels need to be in order to afford effective protection to her child when it is born? When is it appropriate to give a would-be mother a booster vaccination before she becomes pregnant? It is not yet possible to give straightforward answers to these questions.

Vaccination against group B haemolytic streptococci (GBHS) infection is not yet possible. However, screening could be provided in the context of the preconception advice system and antibiotic prophylaxis provided where appropriate. Alternatively, expectant mothers could be screened for GBHS as part of the ordinary pregnancy monitoring regime.\textsuperscript{110,111}
Older people

Older people, too, are increasingly seen as a target group for programmatic vaccination. The number of vaccinations available against conditions that are dangerous mainly to (older) adults, such as influenza and shingles, is growing. This is likely to lead to older people more often forming an explicit target group for public vaccination programmes. The conditions against which they might well be vaccinated in the future include pneumococcal infections (using a conjugated vaccine), whooping cough and respiratory syncytial virus infections.

Risk groups and subpopulations

As a public programme, the NIP is geared to protection of the population as a whole. However, if a disease is not evenly distributed through the population, the most efficient way of protecting the whole population may be to focus on the vaccination of more specific target groups or subpopulations. Indeed, the vaccination of infants and young children may be regarded as a form of target-group selection. Most of the NIP’s target diseases are primarily diseases of childhood and/or have serious health implications mainly for children. So the vaccinations provided against these diseases are entirely or predominantly important for children.

5.4 Conclusion

The NIP’s primary objective – protection of the people and society of the Netherlands against serious infectious disease – forms the basis for the selection of vaccinations for inclusion in the programme. For each target disease, the primary objective should be translated into one of three secondary objectives: eradicate, the creation and maintenance of herd immunity, and the protection of as many individuals as possible. Having originally been the sole focus of the NIP, childhood diseases continue to dominate the programme. However, the NIP is developing into a public vaccination programme for tackling infectious disease in all age groups. Neonates, adolescents, adults, pregnant women, women who are planning a family, older people and specific risk groups are all now seen as possible target groups for the programme.

The scope that should be sought for any given vaccination depends on the objective of that vaccination: serious diseases affecting the population as a whole are best prevented by universal vaccination, while those affecting only particular groups require a more targeted approach.
Chapter 6

Assessment criteria

6.1 Views on vaccination within a defined group

With a view to ensuring that policy in this field is consistent and reasonable, it is desirable to formulate criteria for the inclusion of vaccinations in the NIP. No defined method for assessing a vaccination’s inclusion credentials has so far been available, either in the Netherlands or elsewhere. However, in certain quarters steps towards the development of such a method have been taken\(^2\),\(^1\) and sets of criteria are available for the assessment of other forms of intervention, such as the screening criteria defined by Wilson and Jungner.

To promote clarity regarding the basis on which vaccinations are included in or excluded from the NIP, the Committee has defined seven inclusion criteria. These criteria are intended to serve as a means of determining whether it is desirable to include a particular vaccination for a particular target group. Identification of the appropriate target group – the entire population, all infants and young children, or one or more specific groups or subpopulations – is critical to any assessment of the effectiveness, acceptability and efficiency of a vaccination. In practice, assessment will sometimes involve examination and comparison of several options, using the seven criteria for guidance. A multi-option assessment needs to look not only at the merits of vaccinating various possible target groups, but also at various possible vaccination schedules.
The criteria are based on two ethical principles: (1) that the best possible protection should be afforded to the population as a whole and (2) that benefit should be fairly distributed across population groups, with protection provided on the basis of need.

In the context of care-sector decisions regarding waiting list issues and such like, the two principles are often in conflict. In the context of a public vaccination programme, however, they tend to be mutually reinforcing. In many cases, vaccination of an entire population group (e.g. all children) is the option that affords the best way of protecting the population and gaining the most health benefit. But it is also the option that provides the fairest distribution of benefit. Furthermore, in situations where it is necessary to focus on particular target groups, it makes sense to protect those groups who are at most risk. As well as being the fairest solution, such an approach usually proves to bring the most benefit for the population as a whole.

The seven criteria and the explanation of them provide a framework for the systematic examination of arguments for and against the inclusion and prioritisation of particular vaccinations within the NIP. Each question is formulated on the assumption that an affirmative answer has been given to the previous one. There is nothing to be gained, for example, from considering the effectiveness of a vaccine if the disease that it protects against is either rare or not very serious. And cost-effectiveness need be assessed only if it is clear that the vaccine will be effective and safe when given to the relevant target group. The criteria should not, however, be regarded as a sort of checklist for generating instant answers to NIP inclusion questions. To arrive at a conclusion, it is necessary to carefully assess the available scientific information in order to decide whether each criterion is satisfied. Furthermore, judgements on the desirability of inclusion are always qualified: almost no vaccine is 100 per cent effective or entirely without side-effects. The situation will be even more complex whenever several options are under consideration, each with its own pros and cons.

It is therefore pertinent to ask who should perform the assessment. The Committee believes that responsibility should lie with an independent body, such as the Health Council, that has no interest in the outcome and is not involved in vaccination programme implementation.
6.2 The seven criteria

6.2.1 Summary

The seven criteria are set out below, grouped under five thematic headings. In the following subsections, each criterion is considered in detail.

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. 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 symptoms.
   • The necessary vaccination rate is attainable (if eradication 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.
Priority of the vaccination

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

6.2.2 Seriousness and extent of the disease burden

The provision of vaccination through a public programme must imply the existence of a public health problem that is sufficiently serious to necessitate government involvement. Various things may make a problem 'serious'.

A disease is serious for the individual if:
• it can cause death, serious complications and permanent invalidity; and
• prompt diagnosis and appropriate treatment do not provide adequate scope for preventing, correcting or mitigating the disease’s consequences.

A disease is serious for society if:
• the associated annual rates of incidence or mortality are significant;
• it can spread rapidly;
• it can cause a large-scale epidemic;
• it can lead to social disruption;
• there are no practicable alternative means of protecting against it.

A vaccination policy concerned with serious diseases that have the potential to cause substantial health problems for individuals or for society is consistent with a strategy in which public confidence and a high level of acceptance (as reflected in the vaccination rate) are important. Furthermore, the greater the general interest served by vaccination, the greater the justification is for a pro-active policy.

If consideration is being given to providing a new vaccination to a certain target group, there must be clarity concerning the health burden that the vaccination may be expected to prevent or reduce. When assessing the value of continuing an existing vaccination, the disease burden that would arise without vaccination must be quantified. Diphtheria, for example, is a disease that is presently under control in the Netherlands. However, recent events in Eastern Europe have shown that the disease burden associated with diphtheria can increase rapidly if the vaccination rate falls below a critical level. It is therefore reasonable to assume that the potential disease burden associated with diphtheria is considerable, even in the Netherlands.
The disease burden associated with a target condition is important not only in relation to the inclusion or non-inclusion of vaccination against the condition in the NIP. It is also an index of priority for the development of new vaccines.

6.2.3 Effectiveness of the vaccination

Through the NIP, vaccination is provided to apparently healthy people, usually children. In western countries, the use of mass vaccination means that – as long as the vaccination rate remains high – an unvaccinated person’s chances of contracting one of the target diseases and developing complications are small. In other words, vaccination serves to prevent future health impairment that is actually unlikely.

Under such circumstances, the standards of effectiveness and safety that must be met by a vaccine are very high – higher indeed, than those usually applied in the context of therapeutic drugs, since the latter are given to people who are ill. The second and third criteria therefore imply that a vaccination is admissible only if there is adequate scientific evidence of its effectiveness and safety.

A vaccination may be considered effective if, in a well-designed study, it has been shown to substantially reduce disease burden in the target population. Reduced disease burden may be expressed in terms of lower incidence or a major reduction in symptoms. If eradication of the disease or the creation of herd immunity is the objective of vaccination, it should also be apparent that the necessary vaccination rate is attainable.

In many cases, comprehensive and detailed data on a vaccine’s safety are not available until the vaccine has entered large-scale use. It is therefore important to have a system for recording and investigating adverse reactions. Governments, vaccine producers and health professionals have a responsibility to continuously monitor the safety of vaccinations. This responsibility implies not only studying the effectiveness and safety of individual vaccines, but also carrying out fundamental research into the effects of vaccination on the immune system and into any related side-effects.

6.2.4 Acceptability of the vaccination

The acceptability of a vaccination is determined firstly by the associated discomfort. For the children and their parents, the most conspicuous effect of a vaccination is often the direct discomfort it causes. Although generally minor, such discomfort warrants serious consideration because it affects such a large number
of children. The aim must always be to minimise the discomfort associated with vaccination.

On the basis of this criterion, the Committee has previously indicated that, under normal circumstances, the number of injections given to a child should be limited to two per session. Avoiding undue discomfort is not only to the advantage of the children concerned and their parents. It is also in the general interest to ensure that willingness to participate in the NIP – and therefore the vaccination rate – remains as high as possible.

The Committee has arrived at the figure of two injections per session on the basis of expert opinion and feedback from the field, from parents and clinic staff. There is little scientific evidence to support (or, indeed, to contest) the validity of the chosen figure. However, research into the acceptance of multiple injections is important, and the Committee recommends making provision for such research.

Also of relevance in this context is the fairness of the distribution across population groups. It would not be right for one group to bear all the drawbacks of vaccination, while another received all the benefits. As mentioned earlier in this report, it has been suggested that some groups of older children and adults who come into contact with very young infants should be vaccinated against whooping cough, to minimise the risk of the infants becoming infected. Furthermore, Japanese researchers have published findings apparently indicating that vaccinating children against influenza can be effective as a means of protecting older people.113 (The validity of these findings have, it should be pointed out, been challenged by other authors.)

A fair distribution of risk is also important. Universal vaccination against a disease influences the way it spreads. Groups of people that were previously at relatively little risk, such as older people or people who are conscientiously averse to vaccination, could under certain circumstances be placed at increased risk. Vaccination against polio, mumps and rubella is advantageous to unvaccinated people, insofar as they are less likely to be exposed to the virus on account of its reduced circulation. On the other hand, the virus poses a greater risk to such people in the event of exposure, because of the higher average age at the time of infection. Depending on how these advantages and disadvantages weigh up against one another, unvaccinated people may on balance have either a higher or a lower absolute disease burden.

A non-uniform distribution of advantages and disadvantages is not necessarily unacceptable. However, before a vaccine is introduced, it is appropriate to establish whether shifts in the pattern are likely to occur and, if they are, to consider their acceptability. This was also done before the introduction of universal
vaccination against rubella in 1987, for example.\textsuperscript{114} Anyone who is liable to be placed at greater risk by the introduction of a vaccination should, of course, be properly informed.

The Committee sees its role as advising on the content of the NIP from a national perspective. However, fairness considerations are also relevant in an international context. In developing countries, for example, the vaccine development and introduction priorities will not be the same as those in the developed world. Vaccines that could potentially be very important in developing countries may be under-used there due to lack of resources.

6.2.5 Efficiency of the vaccination

Before a vaccination is included in a public vaccination programme, it is necessary to examine the full spectrum of costs, benefits, and positive and negative health implications. If an alternative vaccination schedule or another means of prevention is possible, than it is necessary to compare the various options. Where a new vaccination is under consideration, the comparator is the baseline situation (the situation without vaccination). In the context of such assessments, cost-effectiveness analysis plays an increasingly prominent role. Ideally, such analysis indicates the best way to use financial resources: how to get the most health benefit for every euro spent.

Cost-effectiveness analysis (CEA) involves calculating the cost per case of disease prevented or per life year gained. Cost-utility analysis (CUA) goes a step further, by seeking to quantify health effects corrected for the quality of life and expressed in QALYs: \textit{quality-adjusted life years}. In principle, the technique enables comparison on cost-utility grounds of various forms of intervention, even if quite dissimilar in nature. In the Netherlands, the maximum acceptable cost for a preventive measure is often set at 20 000 euros per life year or QALY gained. The Council for Public Health and Health Care has suggested that a limit of 80 000 euros per QALY gained is appropriate in the context of communally funded care.\textsuperscript{115}

Cost-effectiveness analysis entails the creation of a model that takes account of the following: the epidemiology of the infectious disease, the associated morbidity and mortality, the effectiveness and side-effects of vaccination, and the cost of vaccination and treatment. Where an infectious disease is concerned, the model should also take account of the indirect effects of prevention. Vaccination of a group within the population can, for example, inhibit circulation of the relevant micro-organism, thus reducing the disease’s prevalence among unvaccinated people. The indirect effects of vaccination can be considerable and
therefore make a major difference to the cost-effectiveness calculation. The vaccination of children against pneumococcal infections and the influence of such vaccination on the disease burden among older people are illustrative in this regard.

However, the (static) models in general use take no account of indirect effects. Dynamic models do, but require the input of detailed contact data. In other words, dynamical models are more complex, but more accurately represent the nature of infectious disease. When analysing the cost-effectiveness of infectious disease prevention measures, therefore, dynamical models are preferable. Nevertheless, static models may be adapted for use if the extent of the indirect effects is known. Whatever type of model is used, the essential characteristics of the relevant infectious disease must be adequately represented, otherwise the value of the output will be seriously compromised.

It is sometimes the case that some of the input data needed for modelling are unavailable. There may, for example, be no epidemiological data for the Netherlands, or doubts may exist concerning the risk of communication, the duration of the infectious period or the importance of various transmission routes. In addition, questions may exist concerning the extent to which quality of life may be deemed impaired by manifestation of a disease. It is sometimes possible to adapt the model to suit the available data. If, for example, no data are available regarding the quality of life associated with a given condition (and QALY figures cannot therefore be calculated), the use of data on infections prevented or life years gained is often an acceptable alternative. Furthermore, despite gaps in the input data a good modelling analysis can often provide important insights.

Inevitably, however, a model is always based on certain assumptions. An important tool for gauging the influence of underlying assumptions is (multivariate) sensitivity analysis. This form of analysis allows estimates to be made for a series of assumptions, so that the level of (un)certainty associated with a cost-effectiveness calculation can be determined. A low cost-effectiveness figure involving a high level of uncertainty carried less weight than a high cost-effectiveness figure involving a low level of uncertainty.

One issue that is of particular significance in relation to the use of health-economics models to assess the efficiency of vaccinations is the discount rate. This is the percentage by which costs and health effects are devalued over time. Discounting is intended to reflect people’s temporal preferences.

If costs are incurred, everyone will agree that they should if possible be deferred. In line with this fact, the value of a euro that need not be found for a year is deemed to be 4 per cent less than that of a euro that has to be found imme-
It is harder, though, to take account of temporal preferences in this way where health effects are concerned. Some health economists take the view that exactly the same principle should be applied to the valuation of health effects. Thus, a life year gained now is worth four per cent more than a life year gained next year.

However, the Health Council believes that the discounting of health effects in this way unfairly devalues preventive measures whose impact is significantly delayed. On the grounds of cross-generational solidarity, an argument can be made for not discounting health effects – at least not to the same extent as financial costs and benefits. When performing CUAs for NIP vaccinations, the Health Council has therefore calculated two figures in each case: one based on health effects discounted at an annual rate of 4 per cent, and one based on a zero or 1.5 per cent discount rate. The Health Care Insurance Board’s new Pharmacoeconomic Guidelines recommend a discount rate of 1.5 per cent for the valuation of health effects.117

The Committee regards modelling as a very valuable tool for the comparison of different prevention strategies. It believes that quantitative forecasts of the long-term effects produced by the same methods should be treated with more caution, however. Cost-effectiveness analysis can contribute to coherent and reasonable decision-making, but is not the value-free tool that some people suggest. Shortcomings in the model or the underlying assumptions limit the validity of model output, but are easily overlooked when such output is summarised in the form of a sum per QALY or life year gained.

It is therefore important to bear in mind that CUA has various methodological shortcomings, which inevitably have distribution implications. The shortcomings in question include difficulties associated with the integration of quality and quantity of life, with the summation of QALYs for different people, with the definition of health status by standardised means, with the formulation of a theory regarding health status preferences, with the design of procedures for measuring such preferences, and with the choice of the assessors. These shortcomings are less significant, however, when defining priorities within a particular policy domain, such as vaccination, mainly of young children.116

Finally, it should be pointed out that, when assessing the efficiency of vaccinations, the Committee has attached particular importance to effects on public health. In addition, the Committee takes the view that any appraisal of the relationship between the costs and benefits of a particular vaccination should always be based upon at least one analysis performed by disinterested expert scientists.
6.2.6 Priority of the vaccination

The last of the seven criteria concerns the importance of the vaccination under consideration, relative to other vaccinations that might also be selected for inclusion. Both the financial resources and practical scope for including vaccinations in the programme are finite; priority should therefore be given to those vaccinations that offer the greatest health benefit.

The decisive consideration is whether inclusion of the vaccination in question serves an urgent or potentially urgent public health need. Thus, priority might be given to, for instance, vaccinating for a disease, against which private citizens cannot effectively protect themselves. It is worth clarifying what is meant by ‘potentially urgent’. A vaccination may be deemed to serve a potentially urgent public health need if it prevents a serious public health problem.

6.3 Conclusion

In an earlier report, the Committee has indicated that the NIP should include a moderate range of vaccinations that are judged to be important, effective and safe. Bearing in mind the public nature of the NIP, the factors that determine a vaccine’s suitability for inclusion in a communal vaccination programme have been translated into seven selection criteria. These criteria can be used to support decisions regarding the form and content of the NIP. Assessment against each criterion may, however, entail the thorough analysis of scientific data and the evaluation of certain values. Hence, application of the criteria requires considerable skill.
7 New possibilities
8 Composition of the programme
9 Recommendations regarding implementation of the programme

Part III

Options
The future of the National Immunisation Programme: towards a programme for all age groups
Chapter 7

New possibilities

7.1 Advances in the development of vaccines

7.1.1 Traditional methods

The basis of nearly every new vaccine developed since the middle of the twentieth century has been a technological breakthrough. Many barriers that initially seemed insurmountable have been overcome by a combination of conviction and considerable investment of both scientific and financial capital.

Vaccines against influenza and yellow fever were created by cultivating viruses in hens’ eggs. The development of cell cultivation techniques made it possible to produce the oral polio vaccine and others. In the period up to 1970, cell and tissue culture methods were used to produce vaccines against illnesses such as measles, mumps and rubella.

As well as commercial enterprises, public health institutes have played their part in vaccine development. The careful targeting of resources enabled the National Institute of Public health in the Netherlands to develop the DTP-polio combination vaccine relatively early, in about 1960. Combination vaccines have since become a major feature of public vaccination programmes.

In 1979, the analysis of viral antigens and antibody patterns in carriers of the hepatitis B virus led to development of a plasma vaccine against hepatitis B. It subsequently proved possible to significantly improve the quality of hepatitis B
vaccines by using genetic manipulation techniques. By incorporating the gene for the hepatitis B surface antigen – the main component of the vaccine – into a yeast, the pure antigen was produced in large quantities. Genetic manipulation has also been the basis of vaccines against whooping cough (an acellular vaccine), Lyme disease and cholera.

The point has been reached, however, where all the ‘easy’ vaccines have been developed. The challenge now is to find ways of vaccinating against conditions to which lifelong immunity cannot be developed naturally. There is also a need to improve various existing vaccines (see subsection Theoretical advances in immunology). To some extent, these objectives can be realised using existing techniques. In some cases, however, progress will depend upon further scientific and technological breakthroughs.

One recent breakthrough has been the development of conjugated vaccines against *Haemophilus influenzae* type b, pneumococci and meningococci C. On their own, capsule polysaccharides of these bacteria proved not to produce an immune response in young children. However, improved understanding of acquired immunity mechanisms led researchers to try attaching the capsule polysaccharides to proteins, which serve as receptor and recognition points for T cells. In this way it was possible to develop effective vaccines against these conditions.

The development of vaccines against the human papilloma virus (HPV) is also of great potential significance. In the thirty years since it was first suggested that HPV could be one of the causes of cervical cancer, it has become clear that the virus is very closely related to the disease. Over a period typically lasting decades, HPV infection can trigger cervical cancer. Scientists have now succeeded in creating virus-like particles that mimic the immunogenic parts of the virus. Vaccines based on these particles appear to be very effective in preventing HPV infection and the initial stages of cervical cancer. Because there is such a long incubation period between HPV infection and the appearance of associated cancer, only time will tell whether the vaccines also provide effective protection against cervical cancer itself and whether booster vaccination is necessary. Following on from the development of the vaccine against hepatitis B, a globally important cause of liver cancer, the HPV vaccine is the first specifically intended to prevent cancer.

Innovations of the kind described above do not occur spontaneously. The average vaccine takes ten years or more to develop and costs perhaps 250 million euros. Furthermore, an assessment has to be made at the outset as to whether development of the vaccine is technically feasible and financially viable, while
only 5 to 10 per cent of development projects will lead to a usable product. All the others are thwarted by problems that were not foreseen at the start of the process.

### 7.1.2 New techniques

DNA techniques are becoming more and more important in the context of vaccine development and production – and the possibilities afforded by these techniques have so far barely been touched upon. Broadly speaking, DNA techniques can be used in five ways.

First, they can be used to acquire the knowledge needed to develop an effective vaccine. If it is known which gene(s) of a micro-organism are relevant for the acquisition of immunity, DNA techniques can be used to map the gene and if necessary modify it for vaccine development. However, it is not always apparent which are the important genes. Under such circumstances, reverse genetics can be used to determine the functions of particular genes. Reverse genetics is also promising as a means of attenuating viruses for use in living vaccines. This method is currently being used to develop vaccines against, for example, influenza, parainfluenza and respiratory syncytial virus. Attenuated living vaccines are attractive because they lead to broad immunity, i.e. both humoral immunity (B lymphocytes) and cellular immunity (T lymphocytes). Attenuated living vaccines can often also be used to generate mucosal immunity (via the mucous membranes).

The second use of DNA technology involves adding genes that code for protective proteins to the cells of bacteria or yeasts. Following the expression of these genes, the antigens can be harvested and used as non-infectious vaccine. This approach has already been used to produce the recombinant hepatitis B vaccine, and other recombinant vaccines are in prospect.

The third option is to genetically manipulate micro-organisms in such a way that they produce foreign antigens. The living micro-organism can then be used as a vaccine. When the antigen is subsequently released, an immune response follows. In principle, it appears possible to use this approach to create vaccines against various viruses and bacteria. Naturally occurring, non-pathogenic or mildly pathogenic micro-organisms and artificially attenuated micro-organisms are best suited to use as vectors. Examples include living attenuated bovine tuberculosis bacteria (Bacille Calmette-Guérin, BCG), cowpox viruses (vaccinia) and adenoviruses. One potential advantage of this approach is that various genes can be added to a single vector, thus enabling the development of combination vaccines.
Fourth, recombinant DNA techniques can be used to produce vaccines for oral administration. Various probiotics, such as lactobacilli, have been used for some years in the food industry and are known to be safe when ingested in large quantities. Lactobacilli carrying vaccine antigens on their cell walls could in principle be used to make vaccines for large-scale oral administration. Some lactobacilli have immunity-promoting properties. Consequently, lactobacilllic vaccines could be developed, which produced a protective immune response from the mucous membranes (mucosa).

It may also be possible to use plants to create edible vaccines. This would involve engineering recombinant plants that expressed a particular antigen. As yet, the technique is in its infancy and must first overcome the fundamental problem that people have an immunological tolerance of many antigens that enter the body via the digestive system. However, if the approach proves viable, it would enable vaccines to be produced cheaply in large quantities. Before edible plant vaccines can enter use, a great deal of work must be done to demonstrate that they can be effective and safe. Other possible ways of using plants such as maize, tobacco, potatoes and tomato to produce vaccines are currently under investigation.

Finally, DNA techniques can be used to produce DNA vaccines. In existing vaccines, the active component consists of one or more of the proteins characteristic of the relevant micro-organism. However, researchers are currently working on vaccines that use not the proteins themselves, but the DNA that codes for the proteins. The advantages of a DNA vaccine of this kind are primarily technical: it is relatively quick and easy to adjust the composition of the vaccine and production is relatively straightforward. DNA vaccines are also comparatively safe, since – in contrast to the situation with living attenuated viruses or bacteria – there is no risk of disease resulting from genetic change leading to renewed virulence. DNA vaccines are also capable of stimulating the Toll-like receptors of the innate immune system by means of the CpG motives present.

Unfortunately, the development of DNA vaccines has not proceeded as quickly as originally expected. In many cases, it has not proved possible to produce sufficient immunity using a single protein (as a gene product). Furthermore, the results of initial trials with humans were less encouraging than the results of animal studies. Positive results have been obtained, however, using heterologous prime-boost strategies, which involve the administration of DNA followed by a vaccine based on a recombinant virus (vaccinia or adenovirus) that expresses the same antigen.
Despite the mixed results obtained so far, much is still expected of DNA vaccine technology. If the principle can be fully developed, the vaccine development process should be speeded up considerably. For the time being, however, the only DNA vaccines registered for use are animal vaccines, including a vaccine that protects horses against West Nile virus, registered in 2005.

The main obstacle to the development of DNA vaccines for humans is the risk that DNA from the vaccine will nestle in the DNA of the recipient and activate a cancer gene. The actual level of risk can only be ascertained by large-scale administration, which is currently almost impossible under the current rules.

The various new vaccine development techniques are summarised in table 8.

### 7.1.3 Theoretical advances in immunology

The scientific community’s growing understanding of immunity, particularly the way that the innate immune system works, has implications for the development of new vaccines. The existing generation of vaccines was developed by trial and error. In many cases, it is not known exactly how the vaccine works or why it is effective. The adjuvants – substances in the vaccines that enhance the immune response – are often selected for their ability to stimulate antibody production, although there is increasing reason to believe that it is in fact cellular immunity

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Table 8. New vaccine development techniques (Source: 38).

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production of recombinant-protein</td>
<td>Hepatitis B surface antigen, Lyme outer surface protein A, CMV gB protein</td>
</tr>
<tr>
<td>Living recombinant micro-organisms with genes from related pathogens</td>
<td>Dengue-genes in yellow fever-17D, parainfluenza 1+2-genes parainfluenza 3, M. tuberculosis in BCG</td>
</tr>
<tr>
<td>Recombinant vectors with pathogen genes incorporated</td>
<td>HIV, CMV</td>
</tr>
<tr>
<td>Alphavirus replicons</td>
<td>HIV, haemorrhagic fevers</td>
</tr>
<tr>
<td>Non-replicating virus-like particles</td>
<td>HPV, SARS</td>
</tr>
<tr>
<td>Naked DNA plasmids</td>
<td>HIV and others</td>
</tr>
<tr>
<td>Prime-boost strategies with DNA and/or vectors</td>
<td>HIV, malaria, tuberculosis</td>
</tr>
<tr>
<td>Reverse vaccinology</td>
<td>Meningococci B</td>
</tr>
<tr>
<td>Micro-arrays for expression of virulence genes</td>
<td>Various bacterial vaccines</td>
</tr>
<tr>
<td>Synthetic proteins</td>
<td>Cancer, CTL vaccines</td>
</tr>
<tr>
<td>Synthetic polysaccharides</td>
<td>Hib</td>
</tr>
<tr>
<td>Reverse genetics</td>
<td>Influenza, parainfluenza, RSV</td>
</tr>
</tbody>
</table>

Hib = Haemophilus influenzae type b, IPV = inactivated polio vaccine, T = tetanus, d = adult dose diphtheria, CMV = cytomegalovirus, BCG = Bacille Calmette-Guérin, HPV = human papilloma virus, RSV = respiratory syncytial virus, HIV = human immunodeficiency virus, CTL = cytotoxic T-lymphocyte.
that is of most significance. Hence, the existing vaccines and adjuvants (often aluminium) have little influence on innate immune system receptors.

Improved understanding of the way that the innate immune system works can be used to produce more sophisticated vaccines. It is increasingly apparent that the immune system’s control mechanisms are highly complex. Their study therefore requires extensive use of modern analytical technologies, such as DNA techniques (genomics) and protein-chemistry techniques (proteomics).

Most of the vaccines that have so far proved successful provide protection against childhood diseases. The natural contraction of such diseases normally results in permanent and effective immunity. This principle has traditionally underpinned the development of vaccines. Successful traditional vaccines have mostly been based on living attenuated micro-organisms, inactivated whole-cell bacteria or toxins. These relatively straightforward vaccines are intended to stimulate the immune system using appropriate antigens. The specific antibody concentrations have in most cases been found to correlate well with protection.

The development of new or improved vaccines against ‘difficult’ diseases, such as meningococci B infection, malaria, HIV infection, influenza, whooping cough and tuberculosis, constitutes a bigger challenge. In this context, it is not only the composition of the vaccine that matters, but also the way it regulates the immune system. Where combined vaccines are concerned, it is important that no opposing influences are introduced. However, modern understanding of the working of the innate immune system is such that these challenges can be overcome. Success in this regard depends on precise determination of the correlates of protection against the relevant infectious disease. Once the correlates are known, it is possible to define the antigen and adjuvant composition required by a vaccine in order for it to have the desired regulatory effects.

A number of special adjuvants intended to stimulate the Toll-like receptors of the innate immune system are at various stages of development. These include CpG-DNA and monophosphoryl lipid A (MPL). MPL is a chemically modified lipopolysaccharide (LPS). LPS, a component of the cellular whooping cough vaccine, has a positive immunity-promoting effect. MPL has a broadly similar effect, but less serious side-effects.119

7.1.4 New administration methods

Most existing vaccines are administered by injection into the muscle tissue. This practice has a historical basis, but it is not in the muscle tissues that interaction between micro-organisms and the immune system occurs. Following injection, antigens have to travel a considerable distance through the lymph and vascular...
systems to the lymph glands, where they can trigger an immune response. In immunological terms, therefore, muscular injection is not ideal. New vaccine administration methods are consequently desirable.

The use of new administration methods has two potential advantages. First, it should facilitate regulation of the immune response, as with the addition of genes that code for cytokines to DNA vaccines.

Second, it would enable an immune response to be generated at the most appropriate location. In the event of a natural infection, interaction between the invasive micro-organism and the immune system usually occurs in the skin or mucous membranes. To mimic this, vaccines are under development that will be administered cutaneously, nasally or orally. Such mucosal vaccines, as they are known, are intended to trigger a protective response from IgA antibodies in the mucous membranes. Oral vaccines already available include a vaccine against rotavirus-induced diarrhoea, and there are advantages to protecting against influenza and whooping cough by mucosal vaccination. An additional advantage with nasal and oral vaccines is, of course, that no injections are required. Furthermore, with these administration routes there is no competition for inclusion in combination vaccines.

Administration immediately below the skin (intra- or subcutaneous administration) also brings antigens quickly into contact with the dendritic or antigen-presenting cells (APCs) of the innate immune system. APCs travel to the lymph glands, where they set the immune response in motion.

Bioneedles probably work in a similar way. Bioneedles are mini-implants (1 x 15 mm) that are painlessly propelled through the skin. They are made of biological carrier material, loaded with vaccine and dried. Following subcutaneous or intramuscular administration, the carrier material dissolves within a few minutes, thus releasing the vaccine. The function normally performed by reconstitution fluid is taken on by the recipient’s body fluids.

Bioneedles are as yet still under development, but promise to bring significant benefits. Trials have suggested improved antigen stability, greater thermal stability and better immunogenicity than associated with conventional administration (G van de Wijdeven, G Kersten, H Hirschberg and A Kelder, personal written communication 2006). It should in principle also be possible to combine several different antigens or primary and booster vaccines in a single bioneedle, thus reducing the number of treatments needed. Furthermore, the use of bioneedles does not result in puncture wounds and therefore carries no risk of infection from contaminated materials.
The method appears suitable for the administration of numerous vaccinations over a short period of time, as would be necessary in an influenza pandemic. The thermal stability of bioneedles reduces reliance on cooling, which is likely to be a major benefit in the Third World, but could also be advantageous in the west. The main drawbacks of traditional hypodermic administration do not exist with transcutaneous administration using bioneedles. Thus, the system seems to have the potential to substantially alter future vaccination practices.

### 7.1.5 New applications

In the future, vaccines will not only be used to prevent infectious disease. In principle, it is possible to develop a vaccine against any condition in relation to which immunological mechanisms play an important role. A vaccine is a realistic option wherever enough is known about the associated immunological processes and how they may be influenced. Research is presently in progress into the possibility of developing therapeutic vaccines for malignant tumours, autoimmune diseases and various chronic diseases, including dementia. In the longer term, preventive vaccines for such conditions are also conceivable.

### 7.2 Expectations with regard to new vaccines

Reports by the Institute of Medicine and RIVM

Vaccinology is presently going through a period of vigorous development. Since 1985, new vaccines have become available with at least the potential for public programmatic use in the control of *Haemophilus influenzae* type b, hepatitis A, hepatitis B (recombinant), chicken pox, shingles, whooping cough (acellular), meningococci C, influenza (attenuated living), typhus, rotavirus, pneumococci (conjugated), Lyme disease and human papilloma virus (see table 7). Two influential general surveys of what is known concerning existing vaccines are: the Jordan Report (2002) and the reference work by Plotkin and Orenstein.120,121
Advances are therefore being made on numerous fronts. Nevertheless, it remains difficult to predict developments in this field. Consider, for example, the 1985 report by the Institute of Medicine (IoM): although produced by an authoritative body, this report has since proved to have been over-optimistic. The IoM has since published a fresh report, based on a scenario analysis conducted between 1995 and 2000. This report identified twenty-six conditions, for which vaccines could theoretically be developed in the next twenty years. The forecasts were based on feedback from experts, who had been asked to indicate the timescale within which a vaccine could be made available and the likely cost. A cost-utility analysis was performed to estimate the disease burden that each form of vaccination could relieve in the USA, and the associated cost-benefit ratio. The model output was used to classify vaccines by anticipated utility: cost-saving, cost less than $10,000 per QALY, cost $10,000-100,000 per QALY, cost more than $100,000 per QALY.

The findings are summarised in table 10. According to this modelling exercise, cost savings could be achieved in the USA by introducing vaccination against pneumococci (since introduced), influenza, cytomegalovirus and group B haemolytic streptococci. The IoM also forecast that much could be achieved by the use of as yet unavailable therapeutic vaccines against insulin-dependent diabetes mellitus, multiple sclerosis and rheumatoid arthritis.

In 2000, an analysis was also published by the RIVM, which was similar to the IoM analysis in some ways. The RIVM assumed that, in the period up to 2010, new vaccines would become available for meningococci B, respiratory syncytial virus, herpes genitalis and human papilloma virus. Calculations were made of the disease burden that could be alleviated by the general provision of these vaccines and a number of other vaccines then already available but not included in the NIP. Cost-effectiveness figures were also estimated and the viability of including each vaccination in the schedule was assessed.

Vaccines against cytomegalovirus, *Helicobacter pylori*, hepatitis C, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, were not expected before 2010, although the analysis indicated that they could be significant for public health. Disease burdens were calculated in disability-adjusted life years (DALYs), i.e. the sum of the number of lost life years and the number of disease year equivalents. Vaccines whose impact was estimated at less than 300 DALYs per year, or whose cost worked out at more than 100,000 euro per QALY or life year gained, were considered unsuitable for programmatic administration. The other vaccines were classed as potentially suitable for inclusion in the NIP.
According to this analysis, the potential benefits of vaccinating twelve-year-olds against HPV and over-sixty-fives against influenza were sufficient to warrant inclusion in the NIP. Vaccination against pneumococci (infants and toddlers, and...
over-sixty-fives), against meningococci B/C, chicken pox, hepatitis B (twelve-year-olds) and RSV was considered potentially suitable for inclusion in the programme (see table 11).

In its 2000 report, the RIVM did not recommend vaccination against rotavirus infection. Assessment was made on the basis of the rota vaccine available at the time. The fact that rotavirus vaccination appears in the table in three different places reflects the uncertainty that then existed concerning the data required for modelling. In 2000, the vaccine in question was withdrawn from the market because of its association with intussusception (potentially fatal infolding of the bowel). It subsequently proved that the intussusception was not specific to the vaccine, but was connected with the fact that the children who received the vaccine were relatively old. Two new vaccines have since become available.

In 2005 and 2006, the RIVM produced updates to its 2000 report. In these updates, greater emphasis was placed on the properties of the micro-organisms and vaccines, on epidemiological considerations, including the disease burden, on programmatic issues and on international matters; less attention was paid to cost-effectiveness estimates.

Additional observations

The uniform model-based approach used by the Institute of Medicine and the RIVM in their analyses is attractive because it enables comparison. However, the many assumptions necessarily made by the analysts introduce an inevitable element of uncertainty.

In the absence of Dutch data, for example, US data have sometimes been assumed to be valid for the Netherlands. Another shortcoming is that a static model has been used, which takes no account of the particular dynamic properties of infectious disease. The RIVM is currently developing dynamic infectious disease models, but the use of such models is not without its own drawbacks.

The Committee therefore takes the view that the comparison of vaccination efficiency on a uniform numeric basis is often not possible, because of uncertainties associated with the modelling and cost-effectiveness analysis.

### 7.3 Conclusion

DNA techniques now play a major role in vaccine development and production. The vaccines that have been successful to date are mainly those that protect against childhood diseases, to which permanent and effective immunity can be naturally acquired.
The future of the National Immunisation Programme: towards a programme for all age groups

The numbers after the vaccination targets indicate the anticipated recipient age at vaccination; so, for example, herpes genitalis 12 indicates that vaccination against herpes genitalis is envisaged at the age of twelve years; rotavirus 5- indicates that vaccination to prevent rotavirus-induced diarrhoea is envisaged before the age of five years.

The challenge now is to develop new or improved vaccines against ‘difficult’ conditions, such as meningococci B infection, malaria, HIV infection, influenza, whooping cough and tuberculosis. In this context, it is not only the composition of the vaccine that matters, but also the way it regulates the immune system. Researchers are also seeking to use new administration methods, including oral and nasal administration, to enhance control over the immune response. Oral and nasal vaccines and bioneedles offer the prospect of generating an immune response where it is actually required: in the mucous membranes or in the skin. Administration by muscular injection – presently the norm – is not ideal in immunological terms.

Historically, a combination of conviction and major investment has repeatedly overcome apparently insurmountable barriers to further vaccine development. However, the development of vaccines is very hard to predict, since only a minority of projects result in a viable product, and the process often takes longer than originally expected.

### Table 11: NIP candidate vaccinations for 2010, with cost-utility ratings and disease burden prevention potential, as estimated for the Netherlands in 2000, on the basis of scenario analysis by the RIVM.

<table>
<thead>
<tr>
<th>Cost-utility rating</th>
<th>Disease burden prevention potential (DALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100-300</td>
</tr>
<tr>
<td>&lt;10,000 euro per QALY/life year gained</td>
<td>Herpes genitalis 12 (Rotavirus 5-)</td>
</tr>
<tr>
<td>10,000-100,000 euro per QALY/life year gained</td>
<td>(Rotavirus 5-)</td>
</tr>
<tr>
<td>&gt;100,000 euro per QALY/life year gained</td>
<td>-</td>
</tr>
</tbody>
</table>

The numbers after the vaccination targets indicate the anticipated recipient age at vaccination; so, for example, herpes genitalis 12 indicates that vaccination against herpes genitalis is envisaged at the age of twelve years; rotavirus 5- indicates that vaccination to prevent rotavirus-induced diarrhoea is envisaged before the age of five years.
Chapter 8

Composition of the programme

8.1 Survey of existing and possible new vaccinations

The developments described in the previous section and the prognoses published by the Institute of Medicine and the RIVM provide a picture of the vaccinations likely to warrant consideration for programmatic public provision over the next fifteen years. On the following pages, the Committee presents an assessment of the suitability for inclusion in the NIP of the candidate vaccinations identified by the two bodies, plus two other candidates: vaccination against Lyme disease and against HIV infection.

For the purpose of this assessment, the Committee has considered each option against the seven criteria, insofar as data availability permitted. As well as examining the credentials of candidate vaccinations, the Committee has reviewed the merit of retaining the existing vaccinations within the programme. The existing NIP vaccinations are listed in table 12 and the candidate vaccinations in table 13.

After table 12 and 13, the Committee’s assessment of each vaccination option is briefly summarised. More comprehensive assessment findings for each option, tabulated according to the seven criteria, are presented in appendix C.
8.2 Assessment of existing vaccinations

8.2.1 Diphtheria

Vaccination against diphtheria satisfies criteria 1 to 5 and criterion 7. No analysis of the vaccination’s cost-effectiveness (criterion 6) was made at the time of its introduction in the Netherlands. However, given that the vaccination has been very effective and its cost is fairly modest, it is reasonable to assume that the cost-effectiveness ratio is favourable. The Committee accordingly recommends retention of the vaccination. The Committee also recommends active monitoring of protective antibody levels in the population. Periodic revaccination of adults is not, however, necessary under the present conditions.
<table>
<thead>
<tr>
<th>Target condition</th>
<th>Vaccine recipients</th>
<th>Vaccination schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicken pox</td>
<td>All children</td>
<td>Separate vaccine or MMRV vaccine, two doses (14 mths and roughly 2 yrs)</td>
</tr>
<tr>
<td>Shingles</td>
<td>People &gt; 50 yrs</td>
<td>One dose subcutaneously</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>All children</td>
<td>(Two to) three doses at intervals of (1 and) 5 mths, 11 to 12 yrs</td>
</tr>
<tr>
<td>Invasive meningococcal B infection</td>
<td>All children</td>
<td>Three/four doses: 2, (3,) 4 and 11 mths</td>
</tr>
<tr>
<td>Influenza</td>
<td>All children</td>
<td>First year two doses at interval of 1 mth, second year 1 dose, before influenza season, 6 mths-2 yrs</td>
</tr>
<tr>
<td>Influenza</td>
<td>People &gt; 50 yrs</td>
<td>One dose every year before influenza season</td>
</tr>
<tr>
<td>Cancer triggered by HPV infection</td>
<td>All children, or only girls</td>
<td>Three doses at intervals of 1 and 5 mths at 11 to 12 yrs</td>
</tr>
<tr>
<td>Respiratory syncytial virus infection</td>
<td>All children</td>
<td>Not yet known</td>
</tr>
<tr>
<td>Rotavirus-induced diarrhoea</td>
<td>All children</td>
<td>Orally, two doses (GSK) or three doses (SPMSD) at intervals of at least 3 wks in first months of life</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>All children</td>
<td>One dose, intracutaneously at 6 mths</td>
</tr>
<tr>
<td>Herpes simplex virus-type 2 (HSV-2)</td>
<td>All children</td>
<td>Not yet known</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>All children</td>
<td>Two doses at intervals of 6-12 mths during childhood</td>
</tr>
<tr>
<td>Infections with cytomegalovirus</td>
<td>All children, or only girls</td>
<td>Three doses, at 11-12 yrs</td>
</tr>
<tr>
<td>Invasive pneumococcal infection</td>
<td>People &gt; 65 yrs</td>
<td>Not yet known</td>
</tr>
<tr>
<td>Smallpox</td>
<td>All children</td>
<td>One dose, intracutaneously</td>
</tr>
<tr>
<td>HIV infection and aids</td>
<td>All children</td>
<td>Not yet known</td>
</tr>
<tr>
<td>Gastrointestinal ulcers and stomach cancer triggered by <em>Helicobacter pylori</em></td>
<td>All children</td>
<td>Not yet known</td>
</tr>
<tr>
<td>Pelvic inflammatory diseases caused by <em>Chlamydia trachomatis</em></td>
<td>All children</td>
<td>Not yet known</td>
</tr>
<tr>
<td>Gonorrhoea</td>
<td>All children</td>
<td>Not yet known</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>All children</td>
<td>Not yet known</td>
</tr>
<tr>
<td>Group A haemolytic streptococcal infection</td>
<td>All children</td>
<td>Not yet known</td>
</tr>
<tr>
<td>Group B haemolytic streptococcal infection</td>
<td>All women planning a family</td>
<td>Not yet known</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>All children</td>
<td>Three doses at intervals of 1 and 11 mths</td>
</tr>
</tbody>
</table>
8.2.2 Whooping cough

Vaccination against whooping cough satisfies criteria 1 to 5 and criterion 7. No analysis of the vaccination’s cost-effectiveness (criterion 6) was made at the time of its introduction in the Netherlands. However, given that the vaccination has been very effective and its cost is fairly modest, it is reasonable to assume that the cost-effectiveness ratio is favourable. The Committee accordingly recommends retention of the vaccination.

The best way to protect very young infants – the population group most at risk from the disease – remains uncertain. Therefore, in response to an earlier report by the Committee, a study has been set up to gather information about the sources of infections contracted by such very young infants. The results of this study are due for publication at the end of 2007. With a view to reducing circulation of the bacterium in the population, consideration should be given to the revaccination of older children and adults. Vaccination might also be made available through a future preconception consultation scheme to women who are planning a family.

8.2.3 Tetanus

Vaccination against tetanus satisfies criteria 1 to 5 and criterion 7. No analysis of the vaccination’s cost-effectiveness (criterion 6) was made at the time of its introduction in the Netherlands. Again, however, the vaccination has been very effective and its cost is modest. It may therefore be assumed that the cost-effectiveness ratio is favourable. The Committee accordingly recommends retention of the vaccination. The Committee also recommends active monitoring of protective antibody levels in the population. Periodic revaccination of adults is not necessary under the present conditions.

8.2.4 Polio

Vaccination against polio satisfies criteria 1 to 5 and criterion 7. No analysis of the vaccination’s cost-effectiveness (criterion 6) was made at the time of its introduction in the Netherlands. In this case, too, the cost-effectiveness ratio may be assumed to be favourable, since the vaccination has been effective and its cost is quite modest. The Committee accordingly recommends retention of the vaccination. In line with the internationally agreed aim of polio eradication, the Netherlands has a special responsibility to seek to persuade the unprotected risk group
made up of pietistic reformed Christians of the value of vaccination. The Committee advises the continuation and, where possible, the intensification of activities to that end. Periodic revaccination of adults is not necessary under the present conditions.

8.2.5 *Invasive Haemophilus influenzae type b infections*

Vaccination against invasive Haemophilus influenzae type b infections satisfies all seven criteria. The Committee accordingly recommends retention of the vaccination. Although the Committee considers Hib vaccination to be effective, it recommends further research into long-term protection and into interactions with other vaccinations. Information provided to the public should make it clear that meningitis can have other causes, against which vaccination does not presently provide protection.

8.2.6 *Mumps*

Vaccination against mumps satisfies criteria 1 to 5 and criterion 7. No analysis of the vaccination’s cost-effectiveness (criterion 6) was made at the time of its introduction in the Netherlands. Since the vaccination has been very effective and its cost is fairly modest, the cost-effectiveness ratio may be assumed to be favourable. The Committee accordingly recommends retention of the vaccination.

In 2004 and 2005 a number of breakthrough infections involving a special variant of the virus occurred among vaccinated secondary school pupils. The Committee therefore recommends providing for research into genetic variation, with a view to shedding light on the association between strain characteristics and vaccine effectiveness. Further research into the way that the timing of the first and second doses influences the effectiveness of the vaccination is also desirable.

8.2.7 *Measles*

Vaccination against measles satisfies criteria 1 to 5 and criterion 7. No analysis of the vaccination’s cost-effectiveness (criterion 6) was made at the time of its introduction in the Netherlands. Since the vaccination has been very effective and its cost is fairly modest, the cost-effectiveness ratio may be assumed to be favourable. The Committee accordingly recommends retention of the vaccination.
The Committee also advises renewed effort to persuade the unprotected risk group made up of pietistic reformed Christians of the value of vaccination. Because the antibody levels typically found in expectant mothers are low, and primary vaccination is not administered until the age of fourteen months, infants are at serious risk of infection in the event of an outbreak in a community with a relatively low vaccination rate. The Committee would like to see further research to establish how earlier administration – of the first vaccine dose in particular – influences the effectiveness of the vaccination. The effectiveness of adjusting the vaccination schedule should be compared with the option of providing measles vaccination through a preconception consultation scheme to women who are planning a family.

8.2.8 **Rubella**

Vaccination against rubella satisfies criteria 1 to 5 and criterion 7. No analysis of the vaccination’s cost-effectiveness (criterion 6) was made at the time of its introduction in the Netherlands. Since the vaccination has been very effective and its cost is fairly modest, the cost-effectiveness ratio may be assumed to be favourable. The Committee accordingly recommends retention of the vaccination.

The Committee also advises renewed effort to persuade the unprotected risk group made up of pietistic reformed Christians of the value of vaccination. Further research into the way that the timing of the first and second doses influences the effectiveness of the vaccination is also desirable. Consideration should also be given to making vaccination available through a future preconception consultation scheme to women who are planning a family.

8.2.9 **Invasive meningococcal C infection**

Vaccination against invasive meningococcal C infection satisfies all seven criteria. The Committee accordingly recommends retention of the vaccination. Information provided to the public should make it clear that meningitis can have other causes, against which vaccination does not presently provide protection.

8.2.10 **Hepatitis B (children whose mothers are carriers)**

The vaccination of children against hepatitis B if their mothers carry the disease is in fact a form of post-exposure treatment, which has been included in the preventive NIP for pragmatic reasons. Without curative vaccination, such children
have a 15 to 90 per cent chance of developing hepatitis B, a serious infectious disease which normally becomes chronic in sufferers belonging to this population group. The vaccination satisfies criteria 1 to 5 and criterion 7. No analysis of the vaccination’s cost-effectiveness (criterion 6) was made at the time of its introduction in the Netherlands. A cost-effectiveness analysis was made, however, prior to the introduction of vaccination for children from high-risk countries. In view of the findings of that analysis, the Health Council has taken the view that the cost-effectiveness ratio is likely to be favourable. The Committee accordingly recommends retention of the vaccination. Because of the failure to reach enough members of the target group, the Health Council advised in 2003 that a committee should be established to strictly supervise the programme.5

8.2.11 Hepatitis B (children with at least one parent from a high-risk country)

The vaccination of children against hepatitis B if they have at least one parent from a high-risk country satisfies all seven criteria. The Committee accordingly recommends retention of the vaccination. In 2001, the Health Council recommended that the reach of the vaccination scheme and the list of high-risk countries should be reviewed at set intervals.4

8.2.12 Hepatitis B (people in risk groups)

The vaccination of people in risk groups against hepatitis B satisfies criteria 1 to 5 and criterion 7. The RIVM is presently analysing the effectiveness and efficiency of the various programmes of vaccination against hepatitis B (criterion 6), including the vaccination of people in risk groups. Once the RIVM has reported on the matter, the Committee will advise on whether vaccination against hepatitis B should continue to be provided to people from risk groups or to all children.

8.2.13 Tuberculosis (children with at least one parent from a high-risk country)

The vaccination of children against tuberculosis if they have at least one parent from a high-risk country satisfies criteria 1 to 5 and criterion 7. A separate Health Council committee has been set up to assess various aspects of this vaccination programme, including its efficiency (criterion 6). The Committee therefore defers judgement to the other committee, which is due to report shortly.
8.2.14 Influenza (over-sixty-fives)

The vaccination of over-sixty-fives against influenza satisfies all seven criteria. A separate Health Council committee has been set up to advise on which population groups should be targeted for influenza vaccination. The Committee accordingly recommends retention of the vaccination. The Committee defers to the other committee for a detailed exposition of the issues involved.124

8.2.15 Invasive pneumococcal infection (children)

The vaccination of children against invasive pneumococcal infection satisfies all seven criteria. The Committee accordingly recommends retention of the vaccination. The Committee does, however, advise considering the use of alternative vaccines with greater coverage (effectiveness), when they become available. Information provided to the public should make it clear that meningitis can have other causes, against which vaccination does not presently provide protection.

8.3 Assessment of new vaccinations

The Committee’s remit is confined to the assessment of vaccinations for provision through public programmes, such as the NIP. Hence, the Committee has not commented on vaccination in response to disease outbreaks, for travellers, for particular patient groups, or for particular professions. Furthermore, paucity of data has prevented the Committee advising on the programmatic provision of certain vaccinations. In such cases, the Committee has indicated what data are lacking. It should be stressed that, if the Committee considers programmatic provision of a particular vaccine inappropriate or is unable to make an assessment due to lack of data, this does not imply that the Committee is opposed to use of the vaccine in individual cases.

8.3.1 Chicken pox

Although chicken pox affects almost whole cohorts of children, the disease is not normally serious. In the Netherlands, there are up to four chicken pox fatalities a year. Hospital admissions run at 1.3 cases per 100 000 people for chicken pox as a primary diagnosis, and 2.3 per 100 000 for chicken pox as a primary or secondary diagnosis. These figures are lower than in other western countries.125 A recent study of chicken pox-related hospital admissions and complications in
Germany, which focused particularly on the Nordrhein-Westfalen region, found that the illness was considerably more prevalent than in the Netherlands. Furthermore, the German researchers discovered evidence of considerable underreporting.126

The differences can to some extent be explained by the way health care is organised in the two countries. In Germany, children are cared for primarily by paediatricians when ill, whereas responsibility in the Netherlands lies largely with GPs. Also, the average age on infection is lower in the Netherlands than in Germany, and this may contribute to the discrepancies as well.125

Nevertheless, the Committee considers it unlikely that there are in reality major differences in the chicken pox-related disease burden on either side of the Dutch-German border. Research into the apparent differences is therefore considered desirable. It may be that the rates of complications and mortality associated with chicken pox are underestimated in the Netherlands, as a result of the condition not always being recorded by hospitals as an underlying cause. At the Committee’s request, data on chicken pox complications are actively being collected within the Dutch Paediatric Surveillance Unit (NSCK).

It has yet to be satisfactorily demonstrated that the seriousness and the extent of the disease burden are considerable (criterion 1). Hence, the Committee also has concerns as to the acceptability of vaccination (criterion 4). Furthermore, it is not clear how vaccination is likely to influence the dynamic relationship between chicken pox and shingles (criterion 3).127-129 It is possible that universal vaccination against chicken pox could lead to an increase in the incidence of shingles. The Committee takes the view that vaccination against chicken pox would not presently serve any urgent public health need in the Netherlands (criterion 7). It accordingly recommends that the value of vaccination be reassessed once the additional data regarding complication rates currently being collected are available.

8.3.2 Shingles

Shingles is a serious condition (criterion 1) and its prevention by vaccination is therefore potentially worthwhile. However, it is not presently possible to assess whether any of the other criteria for inclusion in the NIP are satisfied. Furthermore, the vaccine is not yet available in the Netherlands and vaccination against shingles would not be easy to incorporate within the existing NIP. The system under which older people are presently vaccinated against influenza by GPs might in due course serve as a model for the vaccination of older people against shingles. The Committee recommends reassessing the situation within two years.
8.3.3 Hepatitis B (all children)

Hepatitis B is a serious disease. However, it is relatively uncommon in north-west Europe (criterion 1). To date, the policy in the Netherlands has been to vaccinate specific target groups, rather than the whole population. This policy has proved very labour-intensive, and it has failed to reach all members of the target groups. The WHO recommends vaccinating all children, even in north-west Europe. Where the Netherlands is concerned, the relatively modest health benefit attainable through universal vaccination (criterion 2) has to be weighed up against possible adverse effects on health (criterion 3) and the discomfort associated with and cost of vaccination (criteria 4, 5 and 6).

The RIVM is currently performing a cost-effectiveness analysis of the policy of targeting risk groups. The Committee advises deferring a decision on future policy until the findings of this study are available. At that point, the Health Council will report on the desirability of universal vaccination against hepatitis B.

8.3.4 Invasive meningococcal B infection

Invasive meningococcal B infection is a serious and sometimes acutely fatal condition. Clusters of infections often have major social repercussions (criterion 1). A vaccine is under development, but not yet available. Assessment against the other criteria is not therefore possible at the present time. Nevertheless, in view of the potential health benefit, the Committee considers the development of a vaccine against invasive meningococcal B infection to be important. A future vaccine should preferably be in the form of a combination vaccine (including vaccine(s) against pneumococci and/or meningococci C). The Committee accordingly recommends promoting the development of a vaccine. The position should be reviewed when significant developments in the above situation occur, and certainly within two to three years.

8.3.5 Influenza (all children)

Influenza is a frequent cause of serious disease and complications in infants and young children (criterion 1). However, there is no convincing evidence that vaccination of this target group is efficacious or effective (criterion 2). The Committee therefore recommends that the universal vaccination of children against influenza should not be included in the programme. The effectiveness of such
vaccination does, however, warrant further study. A separate Health Council committee has been established to look into the question of vaccination against influenza. The Committee defers to the other committee for a detailed exposition of the issues involved.124

8.3.6 Influenza (over-fifties)

Only among people over the age of sixty the frequency of influenza-related serious disease, mortality and complications is clearly elevated (criterion 1), and for this group vaccination would provide considerable health benefit (criterion 2). The Committee therefore recommends reducing the age threshold for influenza vaccination from sixty-five to sixty. A separate Health Council committee has been established to look into the question of vaccination against influenza. The Committee defers to the other committee for a detailed exposition of the issues involved.124

8.3.7 Cancer triggered by HPV infection

Cervical cancer the second most common cancer among women; it causes between two hundred and 250 deaths a year (criterion 1). There is a very close association between cervical cancer and HPV infection. A vaccine has recently become available, which is designed to protect against the two types of HPV known to play a causal role in about 75 per cent of cervical cancer cases diagnosed in the Netherlands.130 Another vaccine may become available in the course of 2007. Vaccination may also be effective against cancers of the vagina, labia, anus and penis. One of the two vaccines is also effective against genital warts.

Vaccination against these conditions is potentially a very significant intervention. However, important questions remain to be answered concerning the effectiveness of the vaccination (criteria 2 and 3). For licensing purposes, assessment is made on the basis of safety and efficacy in relation to intermediate indicators (HPV infection and pre-cancerous growths). Evidence of the vaccination’s effectiveness against cancer itself can only come from monitoring results in the field (post-marketing surveillance). Until the efficacy of vaccination as a means of cancer prevention is known, it is not possible to draw conclusions regarding its acceptability (4 and 5) or efficiency (6).

Furthermore, it is not yet clear how the vaccines are best used. Should both girls and boys be vaccinated? What is the best age for vaccination? It is also important to consider the influence that vaccination may have on the effectiveness and efficiency of the existing cervical cancer screening programme (micro-
scopic analysis of ‘smear’ samples). Many of the issues can be clarified or specified by following up the research into effectiveness and safety and by modelling vaccination strategies and (cost) effectiveness.

In view of the potential health benefit, the Committee regards the development of vaccines against HPV-related cancer as a very important development. The Committee recommends promoting research into the regional distribution of HPV types and public acceptance of the vaccination, as well as the modelling of vaccination strategies. Independent cost-effectiveness analysis is also recommended. Consideration should be given to the establishment of a separate advisory committee to look into this topic.

8.3.8 Respiratory syncytial virus infection

In young children and older people, respiratory syncytial virus (RSV) infection is often followed by infections of the lower respiratory tract, such as pneumonia and bronchiolitis. RSV infection is also the most common cause of hospitalisation among infants and a major cause of disease and death among people with immune disorders and among older people (criterion 1). The development of a safe and efficacious vaccine has to date proved very difficult, however. A trial vaccine proved not to prevent the condition, but to make it more serious.

If a safe and efficacious vaccine does nevertheless become available, the vaccination of expectant mothers through a preconception advice programme may be preferable to the vaccination of neonates – but, of course, only if it can be shown that the maternal antibodies do protect the unborn child.

In view of the potential health benefit, the Committee considers the development of a vaccine against respiratory syncytial virus infection to be important. The promotion of vaccine research is therefore recommended. The Committee also recommends looking into the possibility of making vaccination available to women who are planning a family through a preconception advice programme, as well as to older people. The position should be reviewed when significant developments in the above situation occur, and certainly within two to three years.

8.3.9 Rotavirus-induced diarrhoea

Rotavirus infections cause many, sometimes serious, gastrointestinal infections in infants and young children, leading to numerous hospitalisations (criterion 1). An earlier vaccine against rotavirus-related diarrhoea was removed from the market because of suspected serious adverse reactions.
Two new vaccines have since been developed. No concerns exist regarding the efficacy or safety of these new vaccines. However, few data are available to indicate whether the virus types common in the Netherlands are the types against which the vaccines are efficacious. Such data are needed to assess the effectiveness and efficiency of vaccination (criteria 2 and 6). The RIVM is currently conducting a cost-effectiveness analysis.

In view of the potential health benefit the Committee regards the arrival of vaccines against rotavirus-related diarrhoea as an important development. Once the ongoing cost-effectiveness analysis is complete and other information is available, the Health Council will make a recommendation concerning inclusion in the NIP. The Committee advises providing for research to establish which virus serotypes are circulating in the Netherlands.

8.3.10 **Tuberculosis (all children)**

Universal vaccination against tuberculosis has been assessed in response to the RIVM’s 2000 report, which indicated that roughly 1 400 cases of tuberculosis a year were detected in the Netherlands – a number which fell to 1157 in 2005 (criterion 1). The main tuberculosis risk groups are asylum seekers and migrants. Tuberculosis in these groups could not be prevented by the universal vaccination of children in the established population. Furthermore, among adults tuberculosis primarily causes pulmonary infections, against which the BCG vaccine is largely ineffective (criterion 2). The Committee therefore recommends that universal vaccination against tuberculosis should not be introduced. The issues surrounding tuberculosis vaccination for children with at least one parent from a high-risk country are described in subsection Tuberculosis (children with at least one parent from a high-risk country).

8.3.11 **Herpes simplex type 2 infection**

In the population as a whole, the disease burden associated with herpes simplex type 2 (HSV-2) infections is fairly modest. Furthermore, no vaccine is presently available. The position should be reviewed when significant developments in the above situation occur, and certainly within five years.

8.3.12 **Hepatitis A**

In young children, hepatitis A infection is normally benign. Reduced exposure to the virus in the general population means that fewer and fewer people have natu-
rally acquired immunity. As a result, adults in particular are at increased risk of symptomatic infection, but precise incidence or complication data are lacking (criterion 1). It is unlikely that the infection incidence can be significantly reduced in the Netherlands by vaccination (criterion 2). The Committee does not therefore regard universal vaccination in childhood as appropriate. The programmatic vaccination of children with at least one parent from a country where hepatitis A is prevalent may, however, be justified.

The Committee recommends research to establish the incidence of hepatitis A in the population and the risk of complications. Analysis of the cost-effectiveness of the targeted vaccination of children with at least one parent from a country where hepatitis A is prevalent is also recommended, as an alternative to universal vaccination.131 Once data from such research and analyses are available, the Health Council can advise on the respective merits of universal vaccination and targeted vaccination of the subpopulation.

8.3.13 Cytomegalovirus infection

Cytomegalovirus (CMV) infection is dangerous mainly to pregnant women who have not previously been infected. Infection can lead to death, retardation, deafness or visual impairment in the offspring. Few data are available concerning prevention of the condition in the Netherlands (criterion 1).132 At present there is no vaccine against the condition (criterion 2). The Committee nevertheless regards vaccination as potentially important and accordingly recommends the compilation of data on the disease burden in the Netherlands, particularly in the large cities. Once such data is available, the importance of vaccination should be reassessed.

8.3.14 Invasive pneumococcal infection (older people)

Pneumococcal infections cause considerable morbidity and mortality among older people (criterion 1). Such infections are often a complication of influenza. Research into the effectiveness of vaccination using the polysaccharide vaccine now available has produced conflicting results. In 2003, the Health Council took the view that, on the basis of the data then available, there was no scientific justification for vaccinating against pneumococci as well as against influenza (criterion 2).34 The Committee does not therefore advise vaccinating older people against invasive pneumococcal infection. However, since 2003 new evidence has been published concerning the effectiveness of such vaccination. The Committee accordingly recommends that the Dutch Cochrane Centre be asked to update the
Once that has been done, the Health Council can review its recommendation. Little research has been done into the effectiveness of a conjugated vaccine against invasive pneumococcal infection in older people. The Committee anticipates that such a vaccine would be more effective than the polysaccharide vaccine.

### 8.3.15 Smallpox

Smallpox infections no longer occur naturally anywhere in the world. It is nevertheless conceivable that the smallpox virus could be used by terrorists as a bioweapon. In such an event, ring vaccination would be important. Adverse reactions to the smallpox vaccine are relatively common and can be very serious, however (criterion 3). If smallpox infections were not identified early enough, limited mass vaccination could be necessary in addition to ring vaccination. An alternative vaccine, with less significant side-effects would then be preferable. The Committee advises using the existing vaccine only in an emergency; the adverse reactions are such that universal vaccination is not an option.

### 8.3.16 HIV infection and AIDS

HIV-1 infections cause a great deal of morbidity and mortality around the world. The development of a vaccine against HIV-1 has proved problematic, because the virus interferes with the working of the immune system. To date, it has not proved possible to produce a safe and effective vaccine. Various alternative forms of vaccination are therefore being investigated. Candidate vaccines based on attenuated living virus can afford protection, but there is a serious risk of mutation back to the pathogenic form of the bacterium. An attenuated living virus that requires an external factor such as doxycycline may be viable, however. In view of the potential health benefit, the Committee considers the development of a vaccine against HIV infections and AIDS to be important for the Netherlands.

The Committee recommends the promotion of vaccine research. The position should be reviewed when significant developments in the above situation occur, and certainly within two to three years.
8.3.17  
**Gastrointestinal ulcers and stomach cancer triggered by Helicobacter pylori**

Infection with Helicobacter pylori is a contributory factor in approximately two thousand cases of stomach cancer and fifty thousand gastrointestinal ulcers a year (criterion 1). The incidence of these conditions has been declining in recent years. No vaccine is yet available. Vaccination would interfere with a balance that has existed since an early stage of human evolution. The effect of vaccination on the incidence of reflux oesophagitis and oesophageal cancer is therefore difficult to predict; the possibility of these conditions increasing in incidence cannot be excluded (criterion 3). Antibiotic therapy is an adequate treatment for ulcer complaints and a good alternative to vaccination (criterion 6). The Committee does not regard vaccination against gastrointestinal ulcers and stomach cancer triggered by Helicobacter pylori as a priority. The position should be reviewed when significant developments in the above situation occur, and certainly within five years.

8.3.18  
**Pelvic inflammatory disease attributable to Chlamydia trachomatis**

Chlamydia trachomatis (CT) infection is a major cause of serious pelvic inflammations and female infertility (criterion 1). In view of the potential health benefit, the Committee considers the development of a vaccine against pelvic inflammatory disease attributable to Chlamydia trachomatis to be important. However, the intrinsic difficulty of vaccine development is such that a vaccine is not expected before 2015. The position should be reviewed when significant developments in the above situation occur, and certainly within five years.

8.3.19  
**Gonorrhoea**

Gonorrhoea is a cause of serious pelvic inflammations and female infertility (criterion 1). In view of the potential health benefit, the Committee considers the development of a vaccine against gonorrhoea to be important. No vaccine is yet available, however. The position should be reviewed when significant developments in the above situation occur, and certainly within five years.
8.3.20 **Hepatitis C**

In the general population, hepatitis C virus (HCV) infection is a relatively rare cause of liver conditions and jaundice, possibly leading ultimately to cirrhosis, liver failure and liver cancer (criterion 1). The spread of HCV infections is linked to certain risk factors. The Committee does not therefore consider that universal vaccination would be appropriate. It is in any case unlikely that a vaccine against hepatitis C will be available before 2015. The position should be reviewed when significant developments in the above situation occur, and certainly within five years.

8.3.21 **Group A haemolytic streptococcal infection**

Group A haemolytic streptococcal (GAHS) infection can cause serious and even life-threatening illness, but few data are available regarding the disease burden in the Dutch population, linked to laboratory surveillance.\(^{133}\) It is not therefore possible to quantify the disease burden with confidence (criterion 1). Furthermore, no vaccine is yet available. The Committee recommends further study of the disease associated with GAHS infection. Once the findings of such a study are available, the merit of programmatic vaccination should be reconsidered.

8.3.22 **Group B haemolytic streptococcal infection**

Group B haemolytic streptococci (GBHS) infection among expectant mothers is a major cause of premature birth, and of neonatal sepsis, meningitis and residual problems. No reliable data are available regarding prevention of the condition in the Netherlands; nevertheless, the Committee believes that the disease burden associated with GBHS infection is probably considerable. No vaccine is yet available, however. The established preventive procedure involves the administration of prophylactic antibiotics to expectant mothers who have previously had a child with a GBHS-related condition or who are known to carry GBHS in substantial quantities. Screening of expectant mothers for the bacterium, followed by antibiotic prophylaxis, is already possible and may be an alternative to vaccination (criterion 6).

The Committee recommends investigation of the potential significance of vaccination by modelling as a basis for comparison with the effects of screening expectant mothers. Once the findings of such studies are available, the merit of programmatic vaccination should be reconsidered.
8.3.23 Lyme disease

If untreated, Lyme disease can be very serious; however, its prevention is closely related to risk factors and risk locations (criterion 1). An effective vaccine was available in the USA, but has been withdrawn from the market by the manufacturer. The Committee does not believe that universal vaccination is appropriate.

8.4 Conclusion

The Committee has assessed the fifteen vaccinations currently provided through the NIP and twenty-three ‘candidate’ vaccines against the criteria for inclusion in the NIP. All the existing vaccinations satisfy the criteria, and the Committee therefore recommends their retention in the programme.

Where fifteen of the twenty-three candidate vaccinations are concerned, the committee concluded that the associated disease burden was considerable and that provision of the vaccination in a public programme would therefore be desirable. However, in no case – even where a vaccine is already available – is the committee presently prepared to make an unqualified recommendation that vaccination be included in the programme. Where chicken pox, hepatitis B, intestinal rotavirus infection and cancer resulting from human papilloma virus infection are concerned, the committee believes additional analysis is required in the short term in order to determine the importance and urgency of providing vaccination.
Chapter 9

Recommendations regarding implementation of the programme

9.1 Retention of public confidence

Public confidence in the NIP is very strong, as demonstrated by the vaccination rate, which has quite consistently been very high. Retention of that confidence is essential for the success of the programme. Every effort must therefore be made to reinforce confidence and prevent its erosion.

That is not just a question of appropriate and effective public information activities. Trust has to be earned. This implies, amongst other things, that high standards must be maintained in the fields of effectiveness monitoring and safety. It also implies being open about potential problems and risks, and taking public concerns seriously. Sometimes it will be necessary to moderate any unrealistic expectations that participants may entertain; people should be aware, for example, that vaccination doesn’t in all cases provide a lifelong guarantee against infection.

Furthermore, stability is desirable within the NIP. Major changes to the programme – such as the addition of new vaccinations – should be infrequent. When changes are made, the practical consequences for parents and children, such as the need to attend for additional injections or consultations, should be minimised. Hence, if for example several changes are planned, they should if at all possible be made in one go.
No place for compulsion in the NIP

The NIP serves a public interest: protection of the population and society against serious infectious disease. Everyone benefits from the programme. However, not everyone accepts vaccination. Respect for personal autonomy implies enabling people to make their own decisions; this in turn means that everyone should know that he or she has a choice, and that everyone should be properly informed about the advantages and disadvantages of vaccination. In the context of the NIP as presently structured, it is primarily parental autonomy that has to be respected.

The question of whether compulsion is acceptable – in particular whether parents can justifiably be obliged to have their children vaccinated – was discussed at length following the most recent outbreaks of poliomyelitis. The Health Council’s reports of 1974, 1982 and 1995\(^\text{134-136}\) and the report published by the National Council for Public Health (now: Council for Public Health and Health Care) in 1993\(^\text{137}\) all concluded that compulsion was not an option – partly for pragmatic reasons (how can people be forced to cooperate?) and partly for ethical reasons (respect for parental autonomy). In curative health care, medical intervention against the will of a child’s parents is possible under certain conditions, but only if the child’s life or wellbeing is at serious immediate risk. If a parent declines to have his or her child vaccinated, this rarely results in a serious immediate risk, although it could do so in an epidemic.

In principle, compulsion could serve as a tool not only for the protection of individual children, but also for the realisation of a sufficiently high vaccination rate. Such prioritisation of the communal interest is not out of step with the NIP’s function as a programme for the protection of the population as a whole. However, compulsion is a major infringement of personal autonomy. In the present context, it could be justified only if necessary in order to achieve a high vaccination rate and thus, for example, to serve the public interest in herd immunity. Since there is already a very high level of participation without compulsion, it cannot be said that any such need presently exists. As things stand, therefore, compulsion cannot be justified in the context of the NIP.\(^\text{138,139}\)

Within a communal vaccination programme, conflicts can arise between, on the one hand, the interests of society and, on the other, the freedom of choice and other interests of individual citizens. Because the vaccination rate is presently high, parents can choose to decline vaccination, without putting their children at
serious risk. If, however, parents opted in large numbers for this kind of ‘free riding’, there would be serious implications for population-level immunity.

In other words, the principle of respect for the autonomy of individual citizens, in this case parents, is very important but not inviolable. If the vaccination rate were to fall to the point where communal protection against certain infectious diseases was seriously compromised, it is conceivable that compulsion could become justifiable. However, such a situation is largely hypothetical. If the immediate risk were to rise, the inclination to accept vaccination would probably increase as well. Only if compulsory vaccination were necessary to prevent serious harm to the health of the population as a whole could the principle of voluntary participation be overruled.

Pressure is acceptable, however

Although there is generally no place for compulsion in the NIP, a degree of pressure is brought to bear to persuade people to participate. Parents are actively approached and if necessary reminded about participation. Care practitioners work on the assumption that parents are in favour of vaccination. Indeed, if a parent chooses not to have a child vaccinated, the refusal is not accepted without rejoinder: clinic personnel will often question the parent about the decision. Furthermore, public information material stresses the importance of vaccination and the seriousness of the diseases that the NIP seeks to prevent. Finally, the fact that NIP vaccinations are made available as a single package also constitutes a form of pressure; a parent has little scope for accepting some vaccines and not others.

Is the application of pressure acceptable? Pressure is probably necessary in order to attain and maintain a high vaccination rate. Also, as long as people are free to refuse vaccination, pressure need not be unacceptable. However, any pressure that is brought to bear should always be proportional, and no greater than necessary. Given the importance of retaining public confidence in the NIP, it is also important to be open about the reasons for using pressure. Parents need to be aware that the government regards a high vaccination rate as important because it results in greater protection for the population as a whole.

The NIP’s fixed composition constitutes a de facto form of pressure. There is not a menu system allowing parents to select their preferred vaccination schedule. The scope for choice is limited, which places pressure on parents to accept the whole package. Nevertheless, it is not uncommon for parents to ask clinic staff whether they can decline particular vaccines while accepting the rest, or
whether they can postpone their children’s vaccination. Should practitioners have to comply with such requests?

The answer depends on how, in ethical terms, the provision of vaccination should be regarded. If (the parents of) each individual child has/have a moral right to expect the government to provide vaccination against a number of diseases, then it must be up to each individual how that right is exercised. Under this interpretation, the government has an obligation to provide the relevant vaccines, and cannot make provision conditional upon the acceptance of certain conditions.

However, the NIP’s primary objective is collective: to protect the population as a whole. In a situation where the collective interest prevails, an individual does not necessarily have any right to selective vaccination. It is the government’s responsibility to decide how and when it can most effectively perform its duty to protect the population as a whole. This analysis does not exclude flexibility, but implies that it is justifiable for the government to define the limits of flexibility and reject any form of flexibility that could compromise the high vaccination rate.

If a parent wishes to defer a particular vaccination, the fact that the child will nevertheless be vaccinated in due course is a relevant consideration. Allowing a degree of flexibility in such situations may actually be beneficial for the vaccination rate. The issue of public confidence in the programme is also relevant in this regard. Parents’ concerns about possible adverse reactions should, for example, be taken seriously.

9.3 Monitoring effectiveness and safety

Coherent surveillance programme

Effectiveness and safety monitoring is an essential component of the NIP. Continuous checks should be made to determine whether the programme is achieving its goals and whether any safety problems (adverse reactions) seriously detract from the health benefit. Coordination and systematic working are of particular importance in this context.

The government has given the RIVM’s Centre for Infectious Disease Control (CId) responsibility for such coordination. The CId works with doctors, hospitals and laboratories to operate a coherent surveillance programme, through which the vaccination rate, target diseases, clinical phenomena, micro-organisms and adverse reactions are monitored. As previously indicated, the Committee
believes that the socio-psychological determinants of parents’ inclination to have their children vaccinated should also be monitored.

In 2004, the CIb started actively studying the frequency and nature of adverse reactions to vaccinations provided through the NIP. Particular attention has been given to the vaccination of four-year-olds with the DTP and acellular whooping cough vaccines and to the comparison of reactions to the acellular whooping cough vaccine with reactions to the old cellular vaccine.

In the context of NIP safety monitoring, the Committee regards such targeted active study as an important supplement to the existing passive registration activities. Such an approach is the only way of obtaining reliable information about the frequency and nature of adverse reactions.

**Monitoring of long-term adverse reactions**

Traditional vaccines are made up of numerous proteins (antigens). The large number of proteins involved can contribute to the relative frequency with which short-lived adverse reactions occur. On the other hand, the multiple stimulation of the immune system may protect against unbalanced immunological responses. The use of increasingly pure vaccines could lead to a situation where vaccine proteins produce a selective response in sensitive individuals. Of particular importance in this regard are likely to be the T lymphocyte system and the Toll-like receptors of the innate immune system, as described in section.

Although no clear evidence of this phenomenon has so far been found following administration of current vaccines to people, it has been observed in laboratory animals. If it were to occur in people, it could result in adverse long-term immunological reactions. Because personal genetic characteristics are likely to play a role, such reactions would probably be rare, however.

The Committee considers it very important that the monitoring arrangements for the NIP are designed to allow for the detection of adverse immunological reactions. To this end, it would be necessary to link individual data from the vaccination register to data from disease registers.

**9.4 Enabling focused research**

Following recent technological advances, the pharmaceutical industry is likely to take a renewed interest in the development and production of vaccines. Within the network of national and international assessment bodies, such as the Medicines Evaluation Board (MEB) and the European Agency for the Evaluation of Medicinal Products (EMEA), a vaccine undergoes thorough review before being
allowed onto the market. The manufacturer has to provide the results of extensive detailed research into the efficacy and safety. Part of the assessment process involves considering the effect of using the vaccine at the same time as other common vaccines looking for possible interactions between vaccines.

It is increasingly common for the assessment of vaccines for licensing purposes to be made on the basis of intermediate criteria, i.e. not on the basis of the vaccine’s effect on occurrence of the disease, but on the basis of its effect on an indirect indicator, such as antibody levels. Under such circumstances, final assessment of the vaccine’s effectiveness in large-scale use (phase IV research) takes place in the field, in the form of post-marketing surveillance. This approach was adopted with the vaccines against meningococcal C infection. The development of new vaccines against pneumococcal infections and HPV has since followed a similar pattern. When a vaccine is licensed under such circumstances, it is necessary to specify what the manufacturer’s subsequent responsibilities are.

The inclusion of such vaccines in the NIP raises further questions, since that implies use in the context of a multipart programme. The vaccination schedule followed and other vaccines used in the Netherlands will not necessarily be the same as in the research undertaken by the manufacturer. It is therefore pertinent to ask whether the vaccine can be used in the context of the Netherlands’ established schedule and at the same time as the other vaccines administered here. The product information provided to patients and doctors with all registered vaccines includes information about possible interference. However, if data relevant to the situation that exists in the Netherlands are not available, clinical studies should be performed before the vaccine is used in conjunction with others.

Questions may also arise concerning the particular epidemiological situation in the Netherlands. How effective may vaccination be expected to prove here? Thus, specifically Dutch research may also be needed for the assessment of efficiency under various scenarios. The Committee would wish to have at least one independent cost-effectiveness analysis available to it.

In this context, it is also important to consider whether an abbreviated vaccination schedule – involving fewer injections than prescribed – is possible. This issue recently arose in relation to pneumococcal vaccination. The Health Council was asked to consider the advisability of administering three doses of vaccine instead of four. A ‘three-jab schedule’ has clear advantages over a ‘four-jab schedule’: less inconvenience and discomfort for parents and children; less use of the already stretched programme capacity; and less expense. However, these advantages would count for little if vaccination on an abbreviated schedule did not provide adequate protection.
Following assessment of all the available data, the Council has concluded that there is presently no convincing scientific evidence concerning the effectiveness of a three-jab schedule. Several studies have found that such a schedule does result in the presence of antibodies in the blood, but there are no data from which to ascertain whether those antibodies are sufficient to provide the protection sought. The research results therefore leave considerable uncertainty regarding the actual level of protection afforded to infants. By contrast, the established four-jab schedule is known to be effective. The Health Council has accordingly made a number of recommendations regarding research into abbreviated vaccination schedules. Where pneumococcal vaccination is concerned, the recommendations relate to international research into the clinical effectiveness, and to functional immunological research.

Questions about programmatic issues can be answered only with the aid of specific research. Responsibility for such research lies not with the individual vaccine manufacturer, but at least partially with the Dutch government. The government needs to create an environment in which specifically Dutch research can take place, if the public is to be provided with the best possible protection against infectious disease through the NIP.

In many cases, it will be convenient or even necessary to perform such research within the setting of the NIP. Under such circumstances, steps must be taken to protect the interests of the programme and of individual participants. The NIP should not be used for research that involves considerable or unknown safety risks. Furthermore, research conducted within the setting of the NIP should be of direct relevance to the programme and should satisfy high quality and care standards.

9.5 Encouraging (refresher) training

Many hundreds of people are involved in running the NIP every day. Together, they ensure that the NIP continues to move steadily forward and that a high vaccination rate is achieved. However, although the programme is part and parcel of most people’s lives, it is important to recognise that the modern consumer is entitled – and increasingly inclined – to ask questions about the programme. Child health practitioners must therefore possess not only relevant knowledge, but also various complex skills. This has implications for the way such professionals are trained. Except in the rare cases where vaccination is contraindicated, practitioners need to be able to convince parents of the importance of prompt vaccination. They also need to have the knowledge and communication skills to discuss the associated issues.
With the exception of a few notable initiatives, the training currently provided to clinic staff and doctors makes little provision for these needs. The Committee would therefore like to see further professionalisation of the child health service with regard to interpersonal information communication.

However, health practitioners working in other disciplines would also benefit from (refresher) training. Organisational insularity and the rare nature of medical problems associated with vaccination mean that doctors and nurses working outside the child care service often have insufficient knowledge of vaccines or the way they work. Furthermore, they are not trained to respond adequately to any questions or doubts raised by parents. As vaccination programmes become larger, this situation is increasingly undesirable.

The Committee therefore believes that practitioners in all health care disciplines should receive (refresher) training in vaccinology and interpersonal communication. It is recommended that this issue be systematically addressed in the training of nurses and doctors working in child health care, MDs, GPs, paediatricians and internists.
References


The future of the National Immunisation Programme: towards a programme for all age groups
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The future of the National Immunisation Programme: towards a programme for all age groups


The future of the National Immunisation Programme: towards a programme for all age groups


References


The future of the National Immunisation Programme: towards a programme for all age groups
A Request for advice

B The committee and other experts consulted

C Tables

Annexes
In September 2000, the RIVM published a report entitled *Towards a Dutch National Vaccination Programme for the 21st Century*, which provided an analysis of likely developments in the field of vaccines and vaccination between 2000 and 2020. Each of the vaccines then available or expected to become available was assessed and conclusions drawn about its ability to reduce disease burden, its efficiency and its suitability for inclusion within the NIP. The report also considered whether it was necessary to make changes to the vaccines then included in the NIP and various measures were recommended with a view to maintaining and improving the programme’s results. On 29 September 2000, the Minister of Health, Welfare and Sport asked the Health Council to make an appraisal of the RIVM report, with particular attention to the following matters (letter reference GZB/GZ 2.108.780):

- The desirability of introducing new vaccines to the NIP
- The selection of particular vaccines and combinations of vaccines and the associated adverse reactions
- The age at which vaccines are administered
- The principles applied by the RIVM when calculating the cost-effectiveness of the vaccines
- The publicly acceptable number of injections given in a single session
- The overall number of vaccinations that can be given, bearing in mind the way that the immune system works
- The possibility/desirability of terminating certain NIP activities
In view of the scope of the RIVM report and the advice requested by the minister, the Council was asked to report in phases, addressing first the existing programme and the period up to 2010 and subsequently considering longer-term developments.
The committee members and other experts consulted

Annex B

The committee members and other experts consulted

National Immunisation Programme Review Committee

- Professor E.J. Ruitenberg, *Chairman*
  emeritus professor of immunology; University of Utrecht; professor of international public health; VU University Amsterdam
- D.J.A. Bolscher
  medical adviser to Prepas, the Vaccination Registry for Gelderland and Overijssel-Flevoland, Deventer
- G. van ’t Bosch, *adviser*
  Ministry of Health, Welfare and Sport, The Hague
- Professor W. van Eden
  physician-microbiologist / professor of veterinary immunology; University of Utrecht
- Dr. K. Groeneveld, *adviser*
  medical immunologist; Health Council, The Hague
- Professor R. de Groot
  professor of paediatrics; University of Nijmegen
- S. Hahné, *adviser* (February-September 2006)
  epidemiologist; National Institute of Public Health and the Environment, Bilthoven
- Professor J. Huisman
  emeritus professor of infectious disease control, Rotterdam
The Committee consulted the following people and bodies:

- Dr. T. Allavoine, Aventis Pasteur MSD, Lyon
- B. Bissumbhar, Consultancy Technology Transfer, Utrecht
- Dr. H. Bogaerts, GlaxoSmithKline Biologicals, Rixensart
- Professor P. van Damme, University of Antwerp
- Dr. A. van der Ende, Bacterial Meningitis Reference Centre, Amsterdam
- Dr. B. Fritzell, Wyeth
The committee members and other experts consulted

- M. Girard MD Msc, Versailles
- Dr. D. Goldblatt, University College London Medical School, London
- Professor N. Guiso, Institut Pasteur, Paris
- Professor J.D.F. Habbema, Erasmus Medical Centrum Rotterdam
- L. Hessel MD, Aventis Pasteur MSD, Lyon
- Professor T. Jefferson, Cochrane Vaccines Field, Rome
- Professor P.-H. Lambert, Centre Medical Universitaire de Genève
- Dr. B. Lee, Aventis Pasteur MSD, Lyon
- Dr. E. Miller, Health Protection Agency, London
- Netherlands Vaccine Institute, Bilthoven
- Dutch Association for the Critical Use of Injections, Roosendaal
- Dr. Th. van Oers, Bio Science Application International BV
- Dr. J.T. Poolman, GlaxoSmithKline Biologicals, Rixensart
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- National Institute of Public Health and the Environment, Bilthoven
- Dr. D.M. Salisbury, Department of Health, London
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- Dr. E. Steyerberg, Department of Public Health, Erasmus University, Rotterdam
- H. Villard MD, Aventis Pasteur MSD, Brussels
- Ph. De Wals MD PhD, Institut national de santé publique du Québec, Montréal
- Dr. C.G. Whitney, Centers for Disease Control, Atlanta
- Dr. D. Wood, World Health Organization, Genève

The penultimate draft of this report was submitted for technical comment to the RIVM, the NVI and dr. H.C. Rümke.

Editorial advice: Dr. P. Slot
Secretarial support: D. van Bladel
Layout: M. Javanmardi

The Health Council and interests

Members of Health Council Committees 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 nonethe-
less 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

Tables

Existing vaccinations (tables 14a-b)
Possible new vaccinations (tables 15a-c)
<table>
<thead>
<tr>
<th>Vaccination against</th>
<th>Diphtheria</th>
<th>Whooping cough</th>
<th>Tetanus</th>
<th>Polio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipients</strong></td>
<td>All children</td>
<td>All children</td>
<td>All children</td>
<td>All children</td>
</tr>
<tr>
<td><strong>Vaccination schedule</strong></td>
<td>2,3,4,11 mths, booster 4 yrs</td>
<td>2,3,4,11 mths, booster 4 yrs</td>
<td>2,3,4,11 mths, booster 4 yrs</td>
<td>2,3,4,11 mths, booster 4 yrs</td>
</tr>
</tbody>
</table>

**Background**

| Associated condition(s) | Membranous laryngitis and choking, ulcerating tracheitis, toxic throat oedema, swollen neck, toxic phenomena (heart arrhythmia, convulsions) often following a longer period of 3 to 6 weeks, in which the second mortality peak occurs; skin diphtheria with ulceration (also highly contagious) | Respiratory infection in two stages: first catarrhal (common cold), then weeks to months of characteristic coughing attacks, often at night, followed by vomiting, whooping in older children; among children less than one year old, approx. 1 case in 1000 is fatal, 1 in 500 has residual cerebral damage, 1 on 100 suffers convulsions during attacks; residual problems include bronchiectasis, but not reduced lung function | Painful, generalised muscle spasms, lockjaw; excessive perspiration, fever, heart arrhythmia, abnormal blood pressure; neonatal tetanus | Mainly asymptomatic; asymptomatic carrier-ship; mild symptoms in 5% of cases: in 0.1-1% of cases paralysis, aseptic meningitis or bulbar paralysis |

| Aim of vaccination | Prevention of diphtheria | Prevention of serious forms of whooping cough | Prevention of tetanus | Prevention of polio; eradication |

| Mechanism of communi-cation | Respiratory | Respiratory | Wound infection | Faeco-oral |
| Type of vaccine (producer) | Inactivated purified diphtheria toxin (NVI) | Acellular protein-based vaccine (GSK: pertussis toxin, pertactin, filamentous haemagglutinin; SPMSD: idem + fimbriae) | Inactivated purified tetanus toxin (NVI) | Inactivated polio virus types 1, 2 and 3 (NVI) |

| Date of inclusion in NIP | Large-scale vaccination since 1952, in NIP from 1957 as DTwP (all cohorts born since 1945 invited for vaccination), now as DTaP-polio-Hib | Large-scale vaccination since 1952, in NIP from 1957 as DTwP (all cohorts born since 1945 invited for vaccination), now as DTaP-polio-Hib | Large-scale vaccination since 1952, in NIP from 1957 as DTwP (all cohorts born since 1945 invited for vaccination), now as DTaP-polio-Hib | Since 1957 (all cohorts born since 1945 invited for vaccination), now as DTaP-polio-Hib |
### Tables

**Invasive *Haemophilus influenzae* type b infections**

<table>
<thead>
<tr>
<th>All children 2,3,4,11 mths</th>
<th>All children</th>
<th>All children</th>
<th>All children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meningitis, sepsis, epiglottitis, pneumonia, sinusitis, otitis media, osteomyelitis, cellulitis, arthritis</strong></td>
<td>Acute viral infection of the respiratory tract, salivary glands, testes and ovaries; sometimes pancreatitis and/or meningitis</td>
<td>Fever, nasal catarrh, cough, conjunctivitis and rash; complications: pneumonia (3.8%), encephalitis (0.15%, mortality 0.02%), subacute sclerosing panencephalitis (1:15 000, always fatal)</td>
<td>Almost always benign spotty illness; mainly a problem for pregnant women: infection of the foetus, mainly in first 12 weeks, can lead to congenital rubella syndrome (CRS: blindness, deafness and immune disorders)</td>
</tr>
</tbody>
</table>

**Prevention of invasive Hib infections (incl. meningitis, sepsis, epiglottitis)**

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Respiratory</th>
<th>Respiratory</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated polysaccharide vaccine (SPMSD/NVI)</td>
<td>Attenuated living mumps virus (NVI)</td>
<td>Attenuated living measles virus (NVI)</td>
<td>Attenuated living rubella virus (NVI)</td>
</tr>
</tbody>
</table>

**Prevention of complications and residual problems of mumps (orchitis, meningitis, deafness, sterility in men)**

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Respiratory</th>
<th>Respiratory</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Since 1993, now as DTaP-polio-Hib</td>
<td>Since 1987, as MMR</td>
<td>Since 1976, now as MMR</td>
<td>From 1974 as separate vaccine for 11-yr-old girls, since 1987 as MMR for girls and boys</td>
</tr>
<tr>
<td>Specific problem description</td>
<td>D</td>
<td>aP</td>
<td>T</td>
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<td>------------------------------</td>
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<tr>
<td>Following break-up of USSR, increased risk of import from Eastern Europe, main potential risk to older people (&gt;50 yrs) with low antibody levels</td>
<td>Whooping cough is most serious in very young infants (&lt; ½ yrs), possible increase in such cases due to declining antibody levels in mothers; since 1996 epidemic outbreaks due to reduced effectiveness of the cellular vaccine used until 2004, combined with the specific properties of that vaccine and the selection of circulating bacterium strains that differ from those used to make the vaccine</td>
<td>Netherlands is vulnerable to introduction and spread due to concentrations of unvaccinated people</td>
<td></td>
</tr>
</tbody>
</table>

Assessment

1. Is the disease serious for individuals and does it affect many people?

Yes, diphtheria can be fatal; without vaccination, major epidemics would be possible, causing widespread mortality. The last epidemic in the Netherlands occurred in 1942-1947, causing 224,000 cases of disease (estimated mortality 5%); mortality fell from 600 in 1947, to 230 in 1948, 149 in 1953 and in 1962; the last endemic cases diagnosed 1962-1963; since 1970 only sporadic cases reported.

Yes, whooping cough is dangerous for young children; particularly in young as yet unvaccinated infants, the condition can be serious or fatal; despite vaccination the disease remains endemic in the Netherlands with epidemic outbreaks every 2 to 3 yrs. At the beginning of the 20th century approximately 1000 deaths and 10,000 cases of illness among children per year; by about 1950, mortality had fallen to approximately 100 per year; 1964-1995 six fatalities and low disease burden; since 1996 4,000-10,000 disease cases, 250-500 hospital admissions per year and a total of eight fatalities reported.

Yes, tetanus is often very serious, with a high mortality rate; tetanus is not transmissible from human to human; partly because of vaccination tetanus is now a rare disease; prior to universal vaccination 20-30 cases of disease and mortality per year; now only a handful of cases a year, in unvaccinated or incompletely vaccinated people born before 1945; neonatal tetanus had already ceased to be a problem in the Netherlands before introduction of universal vaccination.

Yes, in 0.1-1% of infections permanent paralysis; difficult to control without vaccination because most infections are subclinical; the epidemics of polio in 20th century probably attributable to improved hygiene and increased average age at time of infection; previously an uncomplicated gastrointestinal infection. At the start of the 20th century, there were major polio epidemics; last national epidemic was in 1956: 2,200 cases of polio (more than 70 deaths); last outbreaks in 1978 (110 cases, 1 death) and 1993 (71 cases, 2 fatalities) among unvaccinated religious objectors.
Recent increase in Hib infections in the UK; possible causes: non-provision in UK of booster vaccination in second year of life or reduced adjuvant effect of acellular whooping cough vaccine relative to earlier cellular vaccine; in the Netherlands since 2002 increase in vaccine failures to 19 in 2005 and invasive infections to 49 in 2004; occurrence of meningitis attributable to other pathogens could undermine confidence in NIP of parents who are unaware that the condition can have various causes.

Eradication is in principle possible; recent vaccine failures in various European countries, possibly due to disparities between wild strains and vaccine strains.

Netherlands is vulnerable to introduction and spread due to concentrations of unvaccinated people.

CRS is WHO candidate for elimination; Netherlands is vulnerable due to concentrations of unvaccinated people.

Yes, Hib-meningitis has a high mortality rate (2%) and causes serious residual problems (9%); epiglottitis is acutely life-threatening because of choking risk. Prior to universal vaccination, Hib was the main cause of meningitis: approx. 700 cases of invasive infection (meningitis, sepsis) per year, 150-300 hospital admissions; mortality fell from 6 in 1991, to 4 in 1992, 3 in 1993 and 1994 to 1 in 1995.

Yes, although prognosis is generally good, even in the event of encephalitis and serious secondary bacterial infections relatively common; also considerable mortality; reduced infection pressure has led to lower antibody levels in women of childbearing age and thus to elevated risk for neonates.

Yes, congenital rubella syndrome is a serious threat to unborn children; because of universal vaccination, this syndrome has become rare; however, this has led to lower antibody levels in women of childbearing age and thus to elevated risk for unborn children.

Yes, encephalitis and serious secondary bacterial infections relatively common; also considerable mortality; reduced infection pressure has led to lower antibody levels in women of childbearing age and thus to elevated risk for neonates.

Yes, CRS is WHO candidate for elimination; Netherlands is vulnerable due to concentrations of unvaccinated people.

Prior to universal vaccination, everyone had mumps between the ages of 5 and 10 years, 300-800 cases of mumps-related meningitis or encephalitis (0.4-1%), prior to universal vaccination hospital admissions were relatively frequent; since vaccination, the disease has become rare; infections now occur mainly later in life and therefore lead to complications relatively often.

Prior to universal vaccination, everyone had mumps at the age of about 5-10 yrs; hospital admissions for CRS fell from 40 in 1980 to 10 by early 1990s; now less than one case per year; between Sep 2004 and Sep 2005, there was an epidemic mainly involving religious objectors, including 32 pregnant women (15 cases of congenital rubella infection, including 9 cases in which the children had congenital abnormalities associated with the CRS; in two cases was intrauterine foetal death occurred).
<table>
<thead>
<tr>
<th>Table 14a</th>
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<tbody>
<tr>
<td>2. Is the vaccine known to substantially reduce disease burden?</td>
<td>Yes, the vaccination has proved very effective at population level</td>
<td>Yes, in non-Dutch trials, vaccine efficacy was found to be 80-85%; in the Netherlands, effectiveness of the booster at 4 yrs is observable at population level; protection is not permanent, so whooping cough occurs in older children, adults and children who are too young to have been vaccinated; between 1996 and 2005, the vaccine used in the Netherlands was only moderately effective</td>
<td>Yes, the vaccination has proved very effective at population level; litter known about long-term protection</td>
<td>Yes, the vaccination has proved very effective at population level</td>
</tr>
<tr>
<td>3. Do adverse reactions significantly detract from the health benefit attainable?</td>
<td>No, adverse reactions are generally local and transient; the frequency is low</td>
<td>No, adverse reactions are generally local and transient; the frequency is low</td>
<td>No, adverse reactions are generally local and transient; the frequency is low</td>
<td>No, adverse reactions are generally local and transient; the frequency is low</td>
</tr>
<tr>
<td>4. Is the discomfort associated with each separate vaccination in reasonable proportion to the health benefit for the recipient and the population as a whole?</td>
<td>Yes, protection is good and the four primary vaccination doses and the two booster vaccination doses are administered at good intervals</td>
<td>Yes, protection is good and the four primary vaccination doses and the two booster vaccination doses are administered at good intervals</td>
<td>Yes, protection is good and the four primary vaccination doses and the two booster vaccination doses are administered at good intervals</td>
<td>Yes, protection is good and the four primary vaccination doses and the two booster vaccination doses are administered at good intervals</td>
</tr>
<tr>
<td>5. Is the discomfort associated with the vaccination programme as a whole in reasonable proportion to the health benefit for the recipient and the population as a whole?</td>
<td>Yes, the vaccination is part of a combination vaccine; no more than two injections are needed at any one time</td>
<td>Yes, the vaccination is part of a combination vaccine; no more than two injections are needed at any one time</td>
<td>Yes, the vaccination is part of a combination vaccine; no more than two injections are needed at any one time</td>
<td>Yes, the vaccination is part of a combination vaccine; no more than two injections are needed at any one time; unprotected individuals are at greater risk because of the higher average age at the time of infection, but benefit from reduced circulation of the virus brought about by the vaccination programme</td>
</tr>
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<td></td>
<td>B</td>
<td>M</td>
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</tr>
<tr>
<td>Hib</td>
<td>Yes, in non-Dutch trials, vaccine efficacy was found to be 95%; the vaccination has proved very effective at population level; it is not certain that long-term protection is also good, now that circulation of the bacterium has been reduced</td>
<td>Yes, the vaccination has proved very effective at population level</td>
<td>Yes, the vaccination has proved very effective at population level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No, adverse reactions are generally local and transient; the frequency is low</td>
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<td></td>
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<tr>
<td></td>
<td>Yes, protection is good following the since primary vaccination dose; the booster vaccination serves as a backup</td>
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<td>Yes, protection is good following the since primary vaccination dose; the booster vaccination serves as a backup</td>
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<td></td>
<td>Yes, the vaccination is part of a combination vaccine; no more than two injections are needed at any one time</td>
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<td>No, adverse reactions are generally local and transient; the frequency is low</td>
<td></td>
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</tbody>
</table>

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Tables 175
<table>
<thead>
<tr>
<th></th>
<th>D</th>
<th>aP</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Is the ratio between the cost and the health benefit favourable compared with other options for preventive reduction of the disease burden?</td>
<td>No analysis of the vaccination’s cost-effectiveness was made at the time of its introduction in the Netherlands; since the vaccination has been very effective and its cost is fairly modest, the cost-effectiveness ratio may be assumed to be favourable</td>
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<td></td>
</tr>
<tr>
<td>7. Does provision of vaccination presently serve an urgent or potentially urgent public health need?</td>
<td>Yes, diphtheria is a serious and sometimes fatal infectious disease; partly because of vaccination, the disease is now rare; the recent increase in diphtheria in Eastern Europe emphasises the importance of continued vaccination</td>
<td>Yes, whooping cough is mainly serious for very young children; following the introduction of universal vaccination the number of cases fell sharply, but since approx 1980 there has been a global increase due to declining immunity in older children and adults; frequent occurrence despite vaccination means new approach required</td>
<td>Yes, tetanus is a serious infectious disease against which effective and safe vaccination is possible</td>
<td></td>
</tr>
<tr>
<td>Recommendation</td>
<td>Retain in NIP; actively monitor antibody levels in the population; periodic revaccination of adults not necessary under present circumstances</td>
<td>Retain in NIP; consider revaccination of older children and adults or provision in context of preconception consulta- tion system; it remains unclear what should be done to protect very young infants (the group for which the disease is most dangerous); in response to an earlier recommendation by the Committee, research has been started to identify sources of infection of very young infants; results expected late 2007</td>
<td>Retain in NIP; actively monitor antibody levels in the population; periodic revaccination of adults not necessary under present circumstances</td>
<td>Retain in NIP; seek to persuade unprotected risk group of value of vaccination; periodic revaccination of adults not necessary under present circumstances; in line with the internationally agreed aim of polio eradication, the Netherlands has a special responsibility to seek to persuade the unprotected risk group made up of conscientious objectors of the value of vaccination; continue and, where possible, intensify activities to that end</td>
</tr>
</tbody>
</table>

The future of the National Immunisation Programme: towards a programme for all age groups
Yes, on introduction, and at a cost of NLG 15 (EUR 6.75) per dose, the Health Council estimated the cost per life year gained at less than NLG 25 000 (EUR 7 500).

B
No analysis of the vaccination’s cost-effectiveness was made at the time of its introduction in the Netherlands; since the vaccination has been very effective and its cost is fairly modest, the cost-effectiveness ratio may be assumed to be favourable.

M
No analysis of the vaccination’s cost-effectiveness was made at the time of its introduction in the Netherlands; since the vaccination has been very effective and its cost is fairly modest, the cost-effectiveness ratio may be assumed to be favourable.

R
No analysis of the vaccination’s cost-effectiveness was made at the time of its introduction in the Netherlands; since the vaccination has been very effective and its cost is fairly modest, the cost-effectiveness ratio may be assumed to be favourable.

Yes, until the introduction of universal vaccination, Hib was the main cause of meningitis; the number of invasive Hib infections has since fallen sharply.

Yes, mumps could be eliminated by vaccination, but recently outbreaks of mumps in previously vaccinated people have been observed in various countries.

Yes, mortality due to measles is about 1‰ and complications are relatively common; Netherlands is vulnerable due to concentrations of unvaccinated people, low antibody levels in expectant mothers and late age of first vaccination; in principle, it should be possible to eliminate measles.

Yes, although rubella is usually benign, it can cause CRS (a serious condition) in unborn children; Netherlands is vulnerable due to concentrations of unvaccinated people and low antibody levels in expectant mothers; the WHO has identified CRS as a candidate for elimination.

Retain in NIP; investigate whether duration of protection (immunological memory) is adequate given reduced circulation of the bacterium; investigate possible interference with other vaccinations; educate the public about other causes of meningitis.

Retain in NIP; increase efforts to persuade unprotected risk group of value of vaccination; study genetic variation in order to improve understanding of relationship between interstrain variation and vaccine efficacy; further research into contribution of different timing of first and second doses to effectiveness of the vaccination.

Retain in NIP; increase efforts to persuade unprotected risk group of value of vaccination; further research into contribution of earlier administration, particularly of first dose, to effectiveness; compare effectiveness of different vaccination schedule and option of providing measles vaccination in context of preconception consultation system.

Retain in NIP; increase efforts to persuade unprotected risk group of value of vaccination; study how timing of first and second doses influences effectiveness; consider revaccination of women of childbearing age in context of preconception consultation system.
<table>
<thead>
<tr>
<th>Vaccination against</th>
<th>Invasive meningococcal C infection</th>
<th>Hepatitis B</th>
<th>Hepatitis B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipients</td>
<td>All children</td>
<td>Children of carriers</td>
<td>Children with at least one parent from a high-risk country</td>
</tr>
<tr>
<td>Vaccination schedule</td>
<td>14 mths</td>
<td>1989-1999: 3, 4, 5 and 11 mths; 1999-2003 2, 3, 4 and 11 mths; 2003-2006 2, 4 and 11 mths; from 2006 0, 2, 3, 4, 11 mths</td>
<td></td>
</tr>
</tbody>
</table>

**Background**

<table>
<thead>
<tr>
<th>Associated condition(s)</th>
<th>In young children often only serious general illness: meningitis and residual problems (epilepsy, deafness, hydrocephalus), sepsis and residual problems (amputations, organ damage)</th>
<th>Liver conditions and jaundice; occasional acute mortality (&lt;1%); asymptomatic chronic carriership more common in infants (90% more than in older children, 10% in 15-yr-olds); chronic carriership results in liver cirrhosis and cancer in 1 in 5 cases</th>
<th>Liver conditions and jaundice; occasional acute mortality (&lt;1%); asymptomatic chronic carriership more common in infants (90% more than in older children, 10% in 15-yr-olds); chronic carriership results in liver cirrhosis and cancer in 1 in 5 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim of vaccination</td>
<td>Prevention of meningococcal C infection</td>
<td>Post-exposure treatment: prevention of carriership and complications (cirrhosis and cancer of the liver)</td>
<td>Prevention of hepatitis B and complications (carriership, cirrhosis and cancer of the liver)</td>
</tr>
<tr>
<td>Mechanism of communication</td>
<td>Respiratory</td>
<td>Mother to child</td>
<td>Intensive contact with carrier</td>
</tr>
<tr>
<td>Type of vaccine (producer)</td>
<td>Conjugated polysaccharide vaccine (various producers)</td>
<td>Recombinant subunit vaccine (HBsAg; various producers)</td>
<td>Recombinant subunit vaccine (HBsAg; various producers)</td>
</tr>
<tr>
<td>Date of inclusion in NIP</td>
<td>Since 2002, as separate vaccine; scheme modified in 2003; from 2006 as DTaP-polio-Hib-HepB</td>
<td>Since 1989, as separate vaccine; scheme modified in 2003; from 2006 as DTaP-polio-Hib-HepB</td>
<td>Since 2003, as separate vaccine; from 2006 as DTaP-polio-Hib-HepB</td>
</tr>
<tr>
<td>Specific problem description</td>
<td>Prolonged protection necessary because of the large age range at risk of infection; occurrence of meningitis attributable to other pathogens could undermine confidence in NIP of parents who are unaware that the condition can have various causes</td>
<td>Curative programme, included within NIP for pragmatic reasons, coverage presently insufficient; a recent evaluation by TNO revealed that a third of recipients are vaccinated at an inappropriate time</td>
<td></td>
</tr>
</tbody>
</table>
assessment of these vaccinations against criteria for inclusion in public vaccination programmes – continued

<table>
<thead>
<tr>
<th>Hepatitis B</th>
<th>Tuberculosis</th>
<th>Influenza</th>
<th>Invasive pneumococcal infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk groups: homosexual men, injecting drug users, promiscuous heterosexuals</td>
<td>Children with at least one parent from a high-risk country</td>
<td>Older people</td>
<td>All children</td>
</tr>
<tr>
<td>Three doses at intervals of 1 and 5 mths respectively</td>
<td>6 mths, intracutaneously</td>
<td>One dose every year before influenza season</td>
<td>2, 3, 4 and 11 mths</td>
</tr>
</tbody>
</table>

**Liver conditions and jaundice; occasional acute mortality (<1%); asymptomatic chronic carriership in adults (2-10%); chronic carriership results in liver cirrhosis and cancer in 1 in 5 cases**

- In young children often asymptomatic infection of lymph glands in mediastinum or non-infectious pulmonary infection; meningitis, sepsis and other forms of extrapulmonary tuberculosis can be dangerous, however
- Influenza; viral pneumonia; various conditions affecting the heart, brain, liver, and kidneys; main complication: pneumonia due to secondary bacterial infection; risk groups are older people and people with pulmonary disease, cardiovascular disease or diabetes; in winter considerable over-mortality among older people
- Diseases of the mucous membranes: inflammation of the middle ear, sinusitis, bronchopneumonia; invasive bacteremia-related diseases: sepsis, pneumonia and meningitis

**Prevention of hepatitis B and complications (cirrhosis and cancer of the liver)**

<table>
<thead>
<tr>
<th>Sexual, blood-blood contact</th>
<th>Respiratory</th>
<th>Respiratory</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant subunit vaccine (HBsAg: various producers)</td>
<td>Living attenuated bovine tuberculosis bacteria (Bacille Calmette-Guérin, BCG, NVI)</td>
<td>Inactivated vaccine (various producers)</td>
<td>Conjugated polysaccharide vaccine, 7-valent available (Wyeth; coverage 59-67% of invasive pneumococcal conditions), 10-valent vaccine GSK possibly available in 2008 (±78%), 13-valent vaccine Wyeth ±2010</td>
</tr>
<tr>
<td>N/a</td>
<td>Not provided through NIP, but through regional scheme by municipal health services/ tuberculosis prevention groups, as separate vaccine</td>
<td>National Influenza Prevention Programme since 1997, provided locally by GPs, GP nurses and in-house doctors, as separate vaccine</td>
<td>Since 2006</td>
</tr>
</tbody>
</table>

**Approaching people at elevated risk of infection (homosexual men, injecting drug users, promiscuous heterosexuals) is very labour-intensive and probably not all target population is reached**

- Annual fluctuations in virulence and degree of match between circulating strains and vaccine strains means generally valid estimates of disease burden and vaccine effectiveness are difficult to make
- Was not well known to general public; introduction in mid-2006 therefore carefully supervised; occurrence of meningitis attributable to other pathogens could undermine confidence in NIP of parents who are unaware that the condition can have various causes
<table>
<thead>
<tr>
<th>Assessment</th>
<th>MenC</th>
<th>HepB (children of carriers)</th>
<th>HepB (children of high-risk countries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the disease serious for individuals and does it affect many people?</td>
<td>Yes, can be serious and acute; residual problems common; clustering has major social repercussions. Between 1999 and 2001, recorded patient numbers rose from 50-100 per yr to 200-300 per yr; peaks in children 0-5 yrs and 15-18 yrs; incidence in 2001 1.7/100 000, following introduction vaccination fell to 0.3/100 000 in 2003; vaccination prevents approx. 20 fatalities and 10 cases of serious residual problems.</td>
<td>Yes, particularly if it occurs early in life, infection often becomes chronic with a risk of complications and carriernesship; carriernesship leads to further spread. At least 1 000 children a year born to HBsAg-positive mothers (carriers); without vaccination an estimated 300 would be infected and 270 would become carriers; vaccination programme coverage is incomplete, so approx. 200 infections and 180 carriernesship cases are prevented.</td>
<td>Yes, particularly if it occurs early in life, infection often becomes chronic with a risk of complications and carriernesship; carriernesship leads to further spread. Modelling suggests that without vaccination there would be 1 150-2 550 infections in population as a whole, with 90-220 becoming chronic and resulting in carriernesship; of the carriers 27-36% are younger than 15 yrs; vaccination in infancy prevents these problems.</td>
</tr>
<tr>
<td>2. Is the vaccine known to substantially reduce disease burden?</td>
<td>Yes, the vaccination has proved very effective at the population level in the UK, the Netherlands and elsewhere.</td>
<td>Yes, the effectiveness of the vaccination schedules used between 1989 and 2003 and since 2006 are 90-100%, depending on the immune status of the mother; the schedule used between 2003 and 2006 had no scientific basis.</td>
<td>Yes, in non-Dutch trials, more than 95% of infants developed protective antibody levels.</td>
</tr>
<tr>
<td>3. Do adverse reactions significantly detract from the health benefit attainable?</td>
<td>No, adverse reactions are generally local and transient; the frequency is low; in the government-promoted passive safety monitoring of the 2002 (catch-up) campaign, out of a total of nearly 3 million vaccinations, there were 41 reports of a more serious nature (incl. severe local reactions, convulsions, high fever); all the children concerned recovered completely.</td>
<td>No, adverse reactions are generally local and transient; the frequency is low; research into possible association with multiple sclerosis in progress; vaccination prevents a disease burden that far outweighs any possible elevated risk of MS.</td>
<td>No, adverse reactions are generally local and transient; the frequency is low; research into possible association with multiple sclerosis in progress; vaccination prevents a disease burden that far outweighs any possible elevated risk of MS.</td>
</tr>
<tr>
<td>HepB (risk groups)</td>
<td>Tbc (children high-risk countries)</td>
<td>Influenza (older people)</td>
<td>Pn (children)</td>
</tr>
<tr>
<td>-------------------</td>
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</tr>
<tr>
<td>Yes, acute infection can be serious; chronic infection associated with risk of complications; carriership leads to further spread</td>
<td>Yes, often acute, particularly in young children, leading to tubercular meningitis and sepsis; diagnosis difficult and consequently often tardy; between 1993 and 2003, 401 cases of tuberculosis diagnosed in children less than 5 yrs old, including 18 cases of serious post-primary tuberculosis (16 of which involved target-group patients, 5 previously vaccinated) (data NTR/KNCV Tuberculosis Foundation)</td>
<td>Yes, considerable over-mortality during epidemics Annually approx. 2 000 extra deaths mainly involving older people, an estimated 3 713 to 744 hospital days/100 000 older people with and without extra risk factors (cardiovascular disease, pulmonary disease, diabetes)</td>
<td>Yes, can be serious and acute; residual problems common; considerable disease burden Per year 20 fatalities, 80 cases of meningitis, 160 of sepsis and 7 500 of pneumonia in children 0-10 yrs; newly introduced vaccination prevents an estimated 16 fatalities, 56 cases of meningitis, 103 of sepsis, 1 800 of pneumonia and 52 000 of inflammation of the middle ear per year in children 0-10 yrs; vaccination also prevents an estimated 62 fatalities, 29 cases of meningitis and 205 of sepsis in other age groups per year</td>
</tr>
<tr>
<td>Approx. 300 cases of acute (usually transient) infection per year, chronic adult carriership closely linked to immigration from countries where hepatitis B is endemic</td>
<td>Yes, in non-Dutch trials, efficacy was found to be 80 to 100%; almost complete protection was obtained in people who developed antibody levels of more than 10mIE/ml</td>
<td>Yes, meta-analyses of non-Dutch trials found that the efficacy of the vaccination against serious extrapulmonary tuberculosis was roughly 75%</td>
<td>Yes, efficacy depending on factors such as the epidemic strain and vaccine strains; in a Dutch trial involving over-sixties, efficacy against confirmed influenza was 52% (95% RI 39-65)</td>
</tr>
</tbody>
</table>

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Yes, meta-analyses of non-Dutch trials found that the efficacy of the vaccination against serious extrapulmonary tuberculosis was roughly 75%

Yes, efficacy depending on factors such as degree of match between epidemic strain and vaccine strains; in a Dutch trial involving over-sixties, efficacy against confirmed influenza was 52% (95% RI 39-65)

No, adverse reactions are generally local and transient; the frequency is low; research into possible association with multiple sclerosis in progress; vaccination prevents a disease burden that far outweighs any possible elevated risk of MS

No, adverse reactions are generally local and transient; the frequency is low

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No, adverse reactions are generally local and transient; the frequency is low
<table>
<thead>
<tr>
<th>Table 14b</th>
<th>MenC</th>
<th>HepB (children of carriers)</th>
<th>HepB (children high-risk countries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Is the discomfort associated with each separate vaccination in reasonable proportion to the health benefit for the recipient and the population as a whole?</td>
<td>Yes, children more than a year old are effectively protected after a single dose</td>
<td>Yes, this curative vaccination is very important to the individual recipient; the five doses are administered at good intervals; after a full series of injections, protection is very good</td>
<td>Yes, the four doses are administered at good intervals; after a full series of injections, protection is very good; research into the effectiveness of a smaller number of doses is in progress (three doses should be sufficient to provide protection; fourth dose is given for logistic reasons)</td>
</tr>
<tr>
<td>5. Is the discomfort associated with the vaccination programme as a whole in reasonable proportion to the health benefit for the recipient and the population as a whole?</td>
<td>Yes, no more than two injections are needed at any one time</td>
<td>Yes, the doses at 2, 3, 4 and 11 months are part of a combination vaccine; no more than two injections are needed at any one time</td>
<td>Yes, the vaccination is part of a combination vaccine; no more than two injections are needed at any one time</td>
</tr>
<tr>
<td>6. Is the ratio between the cost and the health benefit favourable compared with other options for preventive reduction of the disease burden?</td>
<td>Yes, at the time of introduction, the cost per QALY gained was estimated at EUR 2 100 or 600, assuming a health effects discount rate of 4% or 0% respectively</td>
<td>No analysis of the vaccination’s cost-effectiveness was made at the time of its introduction in the Netherlands; a cost-effectiveness analysis was made, however, prior to the introduction of vaccination for children from high-risk countries. In view of the findings of that analysis, the Health Council has taken the view that the cost-effectiveness ratio is likely to be favourable</td>
<td>Yes, the Health Council estimated the cost of universal infant vaccination against hepatitis B at EUR 9 000-28 000 per life-year gained; the cost-effectiveness ratio of targeted vaccination of children with parents from high-risk countries will be considerably better; the RIVM is presently comparing the cost-effectiveness ratios of the various hepatitis B vaccination strategies by model analysis (results expected early 2007)</td>
</tr>
<tr>
<td>7. Does provision of vaccination presently serve an urgent or potentially urgent public health need?</td>
<td>Yes, the target condition is a serious infectious disease with major social repercussions, against which effective and safe vaccination is possible</td>
<td>Yes, children in the target group are at 15-90% risk of developing hepatitis B, a serious infectious disease which in the vast majority of such children will become chronic; this can be prevented by vaccination in almost all cases</td>
<td>Yes, children in the target group are at elevated risk of acquiring this serious infection, which, because of their age, will often result in carriership; this can be prevented by effective and safe vaccination in almost all cases</td>
</tr>
</tbody>
</table>

**Recommendation**

- Retain in NIP; educate the pub-
- Retain in NIP; strict supervision
- Retain in NIP; review reach of vaccination programme and list of high-risk countries (RIVM)
<table>
<thead>
<tr>
<th></th>
<th>HepB (risk groups)</th>
<th>Tbc (children high-risk countries)</th>
<th>Influenza (older people)</th>
<th>Pn (children)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, the four doses are administered at good intervals; after a full series of injections, protection is very good; research into the effectiveness of a smaller number of doses is in progress.</td>
<td>Yes, vaccination involves a single injection and provides effective protection</td>
<td>Yes, vaccination involves an annual injection and provides adequate protection</td>
<td>Yes, the four doses are administered at good intervals; after a full series of injections, protection is very good; research into the effectiveness of a smaller number of doses is in progress.</td>
<td></td>
</tr>
<tr>
<td>Yes, the vaccination is not administered at the same time as NIP vaccinations</td>
<td>Yes, the vaccination is not administered at the same time as other NIP vaccinations</td>
<td>Yes, the vaccination is not administered at the same time as NIP vaccinations</td>
<td>Yes, no more than two injections are needed at any one time</td>
<td></td>
</tr>
<tr>
<td>Further assessment required; the RIVM is presently comparing the cost-effectiveness ratios of the various hepatitis B vaccination strategies by model analysis (results expected early 2007)</td>
<td>Further assessment required (Health Council BCG Committee)</td>
<td>Yes, various analyses have put the cost per life-year gained at (much) less than EUR 20 000 (Postma e.a. 1820, Reinders 720-6570)</td>
<td>Yes, depending on the health effect discount rate (1.5 or 4.0%) the cost per QALY is put at EUR 10 300-14 500 by the Health Council</td>
<td></td>
</tr>
<tr>
<td>Yes, the target condition is a serious infectious disease, which becomes chronic in nearly 10% of cases; carriage can largely be prevented leads to further spread; this can be prevented by effective and safe vaccination in almost all cases</td>
<td>Yes, the target condition is a serious, often acute and sometimes fatal infectious disease, which can largely be prevented by vaccination</td>
<td>Yes, the target condition is a potentially serious infectious disease, particularly in older people and people with risk factors</td>
<td>Yes, the target condition is a potentially serious infectious disease associated with a large disease burden; it can be prevented by effective and safe vaccination in almost all cases; herd immunity can bring major indirect benefits for unvaccinated age groups, particularly older people</td>
<td></td>
</tr>
<tr>
<td>Await analysis and report by RIVM, Health Council will then prepare separate advisory report</td>
<td>Separate evaluation by Health Council in progress; await outcome</td>
<td>Retain in NIP; Health Council has been asked to advise on reduction of threshold age to 50, and on vaccination of young children and risk groups (see body of report)</td>
<td>Retain in NIP; consider switching to more effective vaccines when they become available; educate the public about other causes of meningitis</td>
<td></td>
</tr>
</tbody>
</table>
### Table 15a: Assessment of candidate vaccinations against criteria for inclusion in public programmes (General sources: previous

<table>
<thead>
<tr>
<th>Vaccination against</th>
<th>Chicken pox</th>
<th>Shingles</th>
<th>Hepatitis B</th>
<th>Invasive meningococcal B infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipients</strong></td>
<td>All children</td>
<td>Older people</td>
<td>All children</td>
<td>All children</td>
</tr>
<tr>
<td><strong>Vaccination schedule(s)</strong></td>
<td>Separate vaccine or BMRV vaccine, two doses (14 mths and roughly 2 yrs)</td>
<td>One dose subcutaneously</td>
<td>As DTaP-polio-Hib-HepB for infants at 2, 3, 4 and 11 mths, or as (two to) three doses at intervals of (1 and) 5 mths at 9 to 12 yrs</td>
<td></td>
</tr>
<tr>
<td><strong>Background</strong></td>
<td>Vesicular illness of the epidermis involving modest general phenomena; vesicles liable to bacterial infection; risk groups for complications: neonates (atrophy, neural conditions), children with immune deficiency (pneumonitis, hepatitis), pregnant women (more serious); reactivation of virus causes shingles, which can again cause chicken pox in children</td>
<td>Pruritus, pain, vesicles and redness in the area served by a cutaneous nerve, particularly on the trunk; sometimes permanent sensory changes and persistent pain in the affected region (postherpetic neuralgia); mainly in older people; shingles is caused by the chicken poxvirus lingering in ganglions</td>
<td>Liver conditions and jaundice; asymptomatic chronic carriership more common in children (10% at the age of 15 yrs) than in adults (4% at 35 yrs and 2% at 55 yrs); chronic carrier- ship results in liver cirrhosis and cancer in 1 in 5 cases</td>
<td>In young children often only serious general illness; sometimes acutely fatal; meningitis and residual problems (epilepsy, deafness, hydrocephalus), sepsis and residual problems (amputations, organ damage)</td>
</tr>
</tbody>
</table>

**Aim of vaccination**
- Prevention of the complications of chicken pox
- Prevention of shingles and postherpetic neuralgia
- Prevention of hepatitis B and complications (cirrhosis and cancer of the liver)
- Prevention of meningococcal B infection

**Mechanism of communication**
- Respiratory
- Re-infection from ganglions
- Sexual, blood-blood contact
- Respiratory

**Type of vaccine and development stage (producer)**
- Attenuated living chicken pox virus, available as separate vaccine (GSK and SPMSD, not registered in NL) and combined as BMRV (idem, European registration expected 2006)
- Attenuated living chicken poxvirus (high dose), phase II, (SPMSD), not registered in NL
- Recombinant subunit vaccine (HBsAg), available (various producers)
- Various candidate vaccines in phase I/II of research based on principle of multivalent outer membrane vesicles (OMV) (NVI, HPA, Chiron, GSK) or recombinant proteins (Wyeth, Novartis); prevention of genetic variation requires modification of vaccine, which may make registration problematic
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Influenza</th>
<th>Influenza</th>
<th>Cancer resulting from HPV infection</th>
<th>Respiratory syncytial virus infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>All children</td>
<td>Over-50s</td>
<td>All children, or girls only</td>
<td>All children</td>
</tr>
<tr>
<td>Doses</td>
<td>Children 6 mths-2 yrs first year One dose every year before two doses at intervals of 1 mth, influenza season second year 1 dose, before influenza season, 6 mths-2 yrs</td>
<td>One dose every year before influenza season</td>
<td>Three doses with intervals of 1 (or GSK vaccine: 2) and 5 (4) mths, at 11 to 12 yrs</td>
<td>N/a</td>
</tr>
</tbody>
</table>

**Influenza; viral pneumonia; various conditions affecting the heart, brain, liver, and kidneys; main complication: pneumonia due to secondary bacterial infection; risk groups are children with pulmonary disease, cardiovascular disease or diabetes**

**Influenza; viral pneumonia; various conditions affecting the heart, brain, liver, and kidneys; main complication: pneumonia due to secondary bacterial infection; risk groups are older people and people with pulmonary disease, cardiovascular disease or diabetes; in winter considerable over-mortality among older people**

**Depending on HPV type involved, genital warts or premalign lesions; such lesions can develop into carcinoma of the cervix, anus, penis**

**Generally mild infection of the upper respiratory tract (common cold), in young children and older people relatively often followed by infection of the lower respiratory tract (pneumonia, bronchiolitis); most common cause of hospitalisation in infants and also an important cause of disease and mortality in people with immune disorders and in older people**

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Respiratory</td>
<td>Sexual</td>
<td>Respiratory</td>
</tr>
<tr>
<td>Inactivated vaccine, various producers</td>
<td>Inactivated vaccine, various producers</td>
<td>Virus like particles (VLPs) produced using DNA recombination techniques, SPMSD vaccine (HPV6+11+16+18 registered, GSK vaccine (HPV16+18) registration expected 2007</td>
<td>Subunit vaccines beyond phase 1 (Wyeth, SPMSD, Pierre Fabre) or phase 2 (Pierre Fabre), attenuated living vaccines (phase 1, NVI, NIH)</td>
</tr>
</tbody>
</table>
Table 15a

<table>
<thead>
<tr>
<th>Specific problem description</th>
<th>Chicken pox</th>
<th>Shingles</th>
<th>HepB (all children)</th>
<th>MenB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiologically linked to shingles; must be assessed in association</td>
<td>Universal vaccination against hepatitis B is a priority for the WHO</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Assessment

1. Is the disease serious for individuals and does it affect many people?

No, although chicken pox affects almost whole cohorts of children, the disease is not normally serious; complications associated with and mortality from chicken pox may, however, be underestimated since chicken pox is not always recorded in hospital records as the underlying cause of complications. 1-4 fatalities reported per year, hospital admissions 1.3/100 000 (primary diagnosis) and 2.3/100 000 (primary and secondary diagnosis), i.e. fewer than neighbouring countries; compared with neighbouring countries, chicken pox age peak low in the Netherlands

Yes, shingles can be serious and debilitating; course is often prolonged. Average of 18 fatalities per year, hospital admissions 2.7/100 000 (primary diagnosis) and 5.4/100 000 (primary and secondary diagnosis)

Yes, acute infection can be serious; in cases of chronic infection, risk of complications; carrier-ship leads to further spread. Approx. 300 cases of acute, usually transient, infection per year (3.1/100 000 in men and 0.9/100 000 in women), chronic adult carriership closely linked to immigration from countries where hepatitis B is endemic

Yes, can be serious and acute; residual problems common; major social repercussions because of clustering. Illness comes in waves, following a cycle of 10-15 yrs: 200-600 cases of invasive disease (meningitis, sepsis) per yr; average 490 per yr between 1993 and 1999; 417 patients in 2000, 421 in 2001, 374 in 2002, 294 in 2003, 238 in 2004 and 207 in 2005; exact number of fatalities not known, but roughly 10%
<table>
<thead>
<tr>
<th>Influenza (all children)</th>
<th>Influenza (&gt; 50 yrs)</th>
<th>HPV</th>
<th>RSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are roughly 100 HPV types, of which at least 13 carcinogenic; major geographical differences in distribution of high-risk (sub-Saharan Africa 18%, Europe 4%); HPV16 and HPV18 cause roughly 2/3 of cervical cancers; inclusion of HPV6 and HPV11 would increase efficacy of vaccine to genital warts; natural course of infection and interaction between types not well understood, spontaneous regression common; causes of malignancy not known; in view of long incubation period, prolonged efficacy is required</td>
<td>Earlier candidate vaccine based on formalin-inactivated virus aggravated condition (enhancement)</td>
<td>Yes, a study by the Julius Centre found that children less than two years old were overrepresented in hospital admissions (79 to 271 per 100 000 people per winter) and in GP consultations (520 to 6578 per 100 000 people per winter); the majority of the children concerned were less than six months old; young children were not overrepresented in the mortality statistics.124</td>
<td>Yes, although disease burden and mortality have been greatly reduced by existing screening programme, they remain considerable; 600-700 women a year develop cervical cancer, 200-250 fatalities; between 1989 and 2003, standardised incidence of cervical cancer fell from 9.1 to 6.2 per 100 000, standardised mortality from 3.3 to 2.0 per 100 000 women</td>
</tr>
<tr>
<td>A study performed for the Health Council by the Julius Centre found that 50 to 65-year-olds were overrepresented in the mortality statistics by between 3.8 and 7.6 per 100 000 people per winter; the overrepresentation was accounted for mainly by people aged between 60 and 65: 7.7 - 16 per 100 000 people per winter, i.e. an overrepresentation of 63 to 132 mortality cases per winter; overrepresentation in hospital admissions of between the penis; incidence of cancer 17.7 and 38.0 per 100 000 people per year (among 60 to 65-is similar to incidence of cervical cancer in men per person per year, i.e. an overrepresentation of 130 - 327 hospital admissions per winter).124</td>
<td>Yes, RSV infection is a major cause of serious pneumonia and hospitalisation in young children</td>
<td>Yes, RSV infection is a major cause of serious pneumonia and hospitalisation in young children; in the period 2000-2004 there were an annual average of 526 hospital admissions involving RSV-related pneumonia and an estimated 1 700 involving RSV-related bronchiolitis in children 0-4 yrs</td>
<td>Yes, a study by the Julius Centre found that 50 to 65-year-olds were overrepresented in hospital admissions (79 to 271 per 100 000 people per winter) and in GP consultations (520 to 6578 per 100 000 people per winter); the majority of the children concerned were less than six months old; young children were not overrepresented in the mortality statistics.124</td>
</tr>
</tbody>
</table>
### Table 15a

<table>
<thead>
<tr>
<th>Question</th>
<th>Chicken pox</th>
<th>Shingles</th>
<th>HepB (all children)</th>
<th>MenB</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Is the vaccine known to substantially reduce disease burden?</td>
<td>Yes, non-Dutch studies have found that vaccine efficacy against serious chicken pox is 90%</td>
<td>Not yet certain; effectiveness was high in a US trial</td>
<td>In non-Dutch trials, protective antibody levels found in more than 95% of infants; potential disease burden reduction in the Netherlands not known</td>
<td>No, assessment not yet possible</td>
</tr>
<tr>
<td>3. Do adverse reactions significantly detract from the health benefit attainable?</td>
<td>Possibly: although adverse reactions are infrequent and are generally localised and transient, it is not yet clear what effect vaccination has on shingles; incidence could rise</td>
<td>Not yet known</td>
<td>Adverse reactions are generally local and transient; the frequency is low; research into possible link to multiple sclerosis ongoing</td>
<td>Assessment not yet possible</td>
</tr>
<tr>
<td>4. Is the discomfort associated with each separate injection in reason-</td>
<td>Not clear: the discomfort is slight, but health benefit is also probably minor; not yet determined; the discomfort associated with a single injection is slight, the potential health benefit is considerable</td>
<td>Not clear: discomfort associated with two or three-dose course of injections is slight, but health benefit is also generally minor</td>
<td>Not clear: discomfort associated with two or three-dose course of injections is slight, but health benefit is also generally minor</td>
<td>Assessment not yet possible</td>
</tr>
<tr>
<td>able proportion to the health benefit for the recipient and the popula-</td>
<td>Assessments not yet possible, because effectiveness not yet determined; discomfort associated with three or four-dose course of injections is slight, health benefit is considerable</td>
<td>Assessment not yet possible, because effectiveness not yet determined; discomfort associated with two or three-dose course of injections is slight, health benefit is considerable</td>
<td>Assessment not yet possible, because effectiveness not yet determined; discomfort associated with two or three-dose course of injections is slight, health benefit is considerable</td>
<td>Assessment not yet possible, because effectiveness not yet determined; discomfort associated with two or three-dose course of injections is slight, health benefit is considerable</td>
</tr>
<tr>
<td>tion programme as a whole?</td>
<td>Assessment not yet possible, because effectiveness not yet determined; discomfort associated with two or three-dose course of injections is slight, health benefit is considerable</td>
<td>Assessment not yet possible, because effectiveness not yet determined; discomfort associated with two or three-dose course of injections is slight, health benefit is considerable</td>
<td>Assessment not yet possible, because effectiveness not yet determined; discomfort associated with two or three-dose course of injections is slight, health benefit is considerable</td>
<td>Assessment not yet possible, because effectiveness not yet determined; discomfort associated with two or three-dose course of injections is slight, health benefit is considerable</td>
</tr>
<tr>
<td>5. Is the discomfort associated with the vaccination programme as a</td>
<td>Not clear: vaccination would involve an additional injection, while health benefit is probably minor; see also criterion 3</td>
<td>Assessment not yet possible, because effectiveness not yet determined; vaccine administered separately from others</td>
<td>Assessment not yet possible, because effectiveness not yet determined; vaccine administered separately from others</td>
<td>Assessment not yet possible, because effectiveness not yet determined; vaccine administered separately from others</td>
</tr>
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<td></td>
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<td>----------------------</td>
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<td></td>
</tr>
<tr>
<td><strong>Influenza</strong></td>
<td><strong>Influenza</strong></td>
<td><strong>HPV</strong></td>
<td><strong>RSV</strong></td>
<td></td>
</tr>
<tr>
<td>(all children)</td>
<td>(&gt; 50 yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No, there is no convincing evidence for efficacy or effectiveness in this target group; also, efficacy depends on the 'match' between vaccine strain and circulating strains, which can vary from year to year.</td>
<td>Reduction probable only in over-60s (efficacy demonstrated in people 18-65 yrs; serious disease burden in over-60s); also, efficacy depends on the 'match' between vaccine strain and circulating strains, which can vary from year to year.</td>
<td>No; although high level of protection afforded against infection and early carcinomatous conditions, research into efficacy against cervical cancer itself still in progress; vaccination may also be effective against cancer of penis and anus.</td>
<td>No, assessment not yet possible</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No, adverse reactions are generally local and transient; the frequency is low.</td>
<td>No, adverse reactions are generally local and transient; the frequency is low.</td>
<td>Safety research so far carried out with this vaccine not extensive (SPMSD 16 000 participants) and involved only short follow-up, but no major safety issues detected; more data needed before vaccination could be considered for inclusion in a public programme; vaccination could create niche for non-vaccine-related HPV types</td>
<td>Assessment not yet possible</td>
<td></td>
</tr>
<tr>
<td>No, because effectiveness not yet proven.</td>
<td>Only in over-60s, because disease burden only significant in this age group.</td>
<td>Assessment not yet possible, because effectiveness not yet determined; duration of protection not yet known, booster injections may be necessary; in a combined vaccination-screening programme, vaccination might prevent many false positive screening results and associated anxiety.</td>
<td>Assessment not yet possible</td>
<td></td>
</tr>
<tr>
<td>No, because effectiveness not yet proven.</td>
<td>Only in over-60s, because disease burden only significant in this age group.</td>
<td>Assessment not yet possible, because effectiveness not yet determined; no other vaccines administered at age 11 to 12 yrs; if decision is taken to introduce general hepatitis B vaccination at that age, possibility of combination vaccine against HPV and hepatitis B should be investigated.</td>
<td>Assessment not yet possible</td>
<td></td>
</tr>
</tbody>
</table>
Table 15a

<table>
<thead>
<tr>
<th>Chicken pox</th>
<th>Shingles</th>
<th>HepB (all children)</th>
<th>MenB</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Is the ratio between the cost and the health benefit favourable compared with other options for preventive reduction of the disease burden?</td>
<td>Further study required; in most studies that considered indirect (non-medical) costs, savings were forecast; benefits consist mainly of reduced loss of parents’ labour productivity</td>
<td>The Health Council estimated the cost of universal infant vaccination against hepatitis B at EUR 9 000-28 000 per life-year gained; the cost-effectiveness ratio of targeted vaccination of children with parents from high-risk countries will be considerably better; the RIVM is presently comparing the cost-effectiveness ratios of the various hepatitis B vaccination strategies by model analysis (results expected early 2007)</td>
<td>Unclear, because of falling number of disease cases; the RIVM has estimated that, given the existing number of disease cases and a vaccine price of EUR 10 per dose, the cost-effectiveness ratio would be EUR 42 000 per QALY</td>
</tr>
<tr>
<td>7. Does provision of vaccination presently serve an urgent or potentially urgent public health need?</td>
<td>No, chicken pox is usually benign; it is unclear how vaccination would influence dynamic relationship between chicken pox and shingles; many parents perceive vaccination to be unnecessary</td>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
</tr>
</tbody>
</table>

**Recommendation**

The Committee recommends reviewing the desirability of inclusion once the additional data on the frequency of complications being collected in 2006-2007 are available.

The Committee considers vaccination against shingles to be potentially valuable, but it is not easily integrated within the existing NIP; review within 2 years.

Await outcome of the cost-effectiveness analysis of risk group policy presently being undertaken by RIVM; Health Council will then report on the desirability of universal vaccination against hepatitis B.

Encourage vaccine development; desirability of inclusion should be reviewed in the event of relevant developments, and certainly within 2 to 3 years.
<table>
<thead>
<tr>
<th>Influenza (all children)</th>
<th>Influenza (&gt; 50 yrs)</th>
<th>HPV</th>
<th>RSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>No, because effectiveness not yet proven</td>
<td>Precise data not available, but it is likely that the cost-effectiveness ratio for over-60s is favourable, since ratio for over-65s is known to be favourable</td>
<td>Further study required; because the existing vaccines contain only two HPV-types, which together cause roughly 75% of all cervical cancer in NL, screening programme must continue; when analysing (cost-)effectiveness, vaccination should be compared with possible improvements to screening programme (HPV-diagnostics, self sampling); the cost-effectiveness ratio of vaccination is not yet known</td>
<td>Assessment not yet possible</td>
</tr>
</tbody>
</table>

Investigate effectiveness of vaccination in this group further; for detailed examination of issues involved see separate Health Council report on influenza vaccination.\(^{124}\)

Reduce threshold for programmatic influenza vaccination to 60 yrs; for detailed examination see separate Health Council report on influenza vaccination.\(^{124}\)

The Committee considers HPV vaccination to be potentially very valuable, but many questions remain open; follow up effectiveness trials with further research and modelling of vaccination strategies (optimum age for vaccination, vaccination of only girls or girls and boys) and cost-effectiveness; such research could answer or clarify some of the questions; the Committee recommends research into the regional spread of HPV types, modelling of vaccination strategies, independent cost-effectiveness analysis and public acceptance of vaccination; in view of the complexity of the issues involved, the Committee recommends establishing a separate advisory committee

Encourage vaccine research; investigate possibility of maternal vaccination, inclusion in preconception consultation scheme and vaccination of older people; review in the event of relevant developments, and certainly within 2 to 3 yrs
<table>
<thead>
<tr>
<th>Vaccination against</th>
<th>Rotavirus-induced diarrhoea</th>
<th>Tuberculosis</th>
<th>Herpes simplex type 2 infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipients</td>
<td>All children</td>
<td>All children</td>
<td>All children</td>
</tr>
<tr>
<td>Vaccination schedule(s) considered</td>
<td>Orally, two doses (GSK) or three doses (SPMSD) at intervals of at least 3 wks in first months of life</td>
<td>One dose, intracutaneously at 6 mths</td>
<td>Assessment not yet possible</td>
</tr>
</tbody>
</table>

**Table 15b** Assessment of candidate vaccinations against criteria for inclusion in public programmes (continued) (General

<table>
<thead>
<tr>
<th>Background</th>
<th>Vaccination against</th>
<th>Rotavirus-induced diarrhoea</th>
<th>Tuberculosis</th>
<th>Herpes simplex type 2 infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated condition(s)</td>
<td>Diarrhoea, fever and vomiting; in serious cases dehydration</td>
<td>Pulmonary tuberculosis, meningitis and other forms of extrapulmonary tuberculosis</td>
<td>Inflammation of mucous membranes, pain, cyst formation and ulceration, mainly in the genital region; in neonates neurological conditions and mortality are possible as a result of damage to brain and organs, mainly if the mother has not previously been infected</td>
<td></td>
</tr>
<tr>
<td>Aim of vaccination</td>
<td>Prevention of serious gastroenteritis in children 0-5 yrs</td>
<td>Prevention of tuberculosis</td>
<td>Prevention of herpes in neonates and of genital infections in adults</td>
<td></td>
</tr>
<tr>
<td>Mechanism of communication</td>
<td>Faeco-oral</td>
<td>Respiratory</td>
<td>Sexual</td>
<td></td>
</tr>
<tr>
<td>Specific problem description</td>
<td>Earlier vaccine against rotavirus infection withdrawn from market due to intussusception (intestinal blockage), subsequently proved to be due mainly to children being vaccinated later; not known which serotypes circulate in NL, worldwide, the G9-serotype is in circulation, but implications not known</td>
<td>Prevention of tuberculosis has been made more important by HIV-epidemic and increase in cases of multi-resistance (MDR-TB)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Disease</th>
<th>Hepatitis A</th>
<th>Cytomegalovirus infection</th>
<th>Invasive pneumococcal infection</th>
<th>Smallpox</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All children</strong></td>
<td>Two doses at intervals of 6-12 mths during childhood</td>
<td>All children, or only girls</td>
<td>Three doses, at 11-12 yrs</td>
<td>One dose, intracutaneously</td>
</tr>
<tr>
<td><strong>Prevention of hepatitis A and complications in adults</strong></td>
<td>Prevention of serious neurological conditions in neonates following infection of the mother during pregnancy</td>
<td></td>
<td>Prevention of bacterial pneumo-</td>
<td>Prevention of smallpox reintroduction</td>
</tr>
<tr>
<td>Faeco-oral</td>
<td>Breastfeeding, horizontal</td>
<td>Respiratory</td>
<td>Prevention of bacterial pneumo-</td>
<td>Prevention of smallpox reintroduction</td>
</tr>
<tr>
<td>Inactivated virus, available (various producers)</td>
<td>Attenuated living and subunit candidate vaccines undergoing phase 1 and phase 2 trials; precise correlates of protection not known; reactivation and infection with other strains despite antibodies; antibodies and cellular immunity reduce seriousness of disease; maternal immunity important</td>
<td>Polysaccharide vaccine, available (SPMSD)</td>
<td>Attenuated living vaccine based on vaccinia (cowpox virus) available (NVI), vaccine based on tissue culture under development</td>
<td>Effectiveness in addition to established influenza vaccination needs to be assessed</td>
</tr>
<tr>
<td></td>
<td>General malaise, jaundice; mainly mild phenomena; in adults sometimes liver failure</td>
<td>Invasive bacteraemia-related diseases: sepsis, pneumonia and meningitis</td>
<td></td>
<td>Effectiveness demonstrated at population level, exact vaccine efficacy not known</td>
</tr>
<tr>
<td></td>
<td>Fever, laryngitis, swollen glands; mainly dangerous in previously uninfected pregnant women, in 10-20% of neonates results in death, retardation, deafness or visual impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sources: previous Health Council reports, 1-7,19,123,142.)
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Rota</th>
<th>Tbc (all children)</th>
<th>HSV-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the disease serious for individuals and does it affect many people?</td>
<td>Yes An estimated annual 67 000 infections (95% RI 40 000-114 000), 2 880 (1920-3520) hospital admissions, approx. 1 death in children 0-4 yrs</td>
<td>Yes In 2000 there were roughly 1 400 cases of tuberculosis and 625 tuberculosis-related hospital admissions, by 2005 the number of new cases had fallen to 1157</td>
<td>Doubtful; annually, there are roughly 5 cases of neonatal herpes; the incidence of genital infections is estimated at 8 700 per year</td>
</tr>
<tr>
<td>2. Is the vaccine known to substantially reduce disease burden?</td>
<td>In non-Dutch trials, efficacy against serious forms of rotavirus-related gastroenteritis was high: 84.7% (GSK) and 98% (SPMSD), difference probably largely due to differences between study populations and different caps being applied to seriousness score; effectiveness depends on serotype and time since vaccination; in second year following vaccination approx. 60%</td>
<td>Very variable, mainly depending on specific vaccine; in non-Dutch trials effectiveness against systemic forms of tuberculosis was high (approx. 75%)</td>
<td>Candidate vaccines to date not effective or only efficacious in people who had no antibodies against HSV-1 (40% of the population)</td>
</tr>
<tr>
<td>3. Do adverse reactions significantly detract from the health benefit attainable?</td>
<td>No, adverse reactions are generally local and transient; the frequency is low</td>
<td>No records kept, local reactions, regional infections swollen lymph glands, mainly associated with incorrect (non-intracutaneous) injection, frequency probably low</td>
<td>Assessment not yet possible</td>
</tr>
<tr>
<td>4. Is the discomfort associated with each separate vaccination in reasonable proportion to the health benefit for the recipient and the population as a whole?</td>
<td>Not clear: the health benefits attainable by use in NL not established</td>
<td>No; although only a single injection is required, the vaccine is not effective against pulmonary tuberculosis</td>
<td>Assessment not yet possible</td>
</tr>
<tr>
<td>5. Is the discomfort associated with the vaccination programme as a whole in reasonable proportion to the health benefit for the recipient and the population as a whole?</td>
<td>Not clear: although there is no conflict with other vaccinations in the programme, the health benefits attainable by use in NL not established</td>
<td>No, although there is no conflict with other vaccinations in the programme, the vaccine is not effective against pulmonary tuberculosis</td>
<td>Assessment not yet possible</td>
</tr>
<tr>
<td>HepA</td>
<td>CMV</td>
<td>Pn (older people)</td>
<td>Smallpox</td>
</tr>
<tr>
<td>------</td>
<td>-----</td>
<td>-------------------</td>
<td>----------</td>
</tr>
<tr>
<td>No, in children hepatitis A does not normally lead to complications. Incidence 2 to 3/100,000 per yr: notification: 0.9 per 1,000 in approx. 400 cases of disease; mainly in children of Turkish and Moroccan parents, average age of patients is rising (men 23 y, women 25.4 y in 2002); only 10% of under-35s have natural acquired immunity.</td>
<td>Yes, pneumococcal infections in older people can be serious or even fatal; however, no precise estimates of disease burden are available; in 2005 there were 2,100 cases of hospitalisation for confirmed pneumococcal pneumonia, approx. 65% involving over-65s, and 65 cases of meningitis in this age group; some estimates are much higher, however: 65,000 pneumonia cases, 23,000 hospital admissions and 10,000 fatalities per yr.</td>
<td>Smallpox has been eliminated, but might be used as a bioweapon, with potentially serious consequences for individuals and society.</td>
<td>Assessment not yet possible.</td>
</tr>
<tr>
<td>In non-Dutch trials efficacy of the vaccine was high (nearly 100%); however, it is unlikely that the incidence of hepatitis A in the Netherlands would be significantly reduced by universal vaccination.</td>
<td>Effectiveness demonstrated at population level, exact vaccine efficacy not known.</td>
<td>Assessment not yet possible; effectiveness not established.</td>
<td>Assessment not yet possible.</td>
</tr>
<tr>
<td>No, adverse reactions are generally local and transient; the frequency is low.</td>
<td>No, adverse reactions are generally local and transient; the frequency is fairly frequent.</td>
<td>Discomfort from single injection minor, but effectiveness not established.</td>
<td>Only under very special circumstances (bioterrorism).</td>
</tr>
<tr>
<td>Universal vaccination serves mainly to protect adults, not child vaccine recipients; it is unlikely that the incidence could be significantly reduced by universal vaccination.</td>
<td>Assessment not yet possible; effectiveness not established.</td>
<td>Although there is no conflict with other vaccinations in the programme, effectiveness not established.</td>
<td>Only under very special conditions (bioterrorism).</td>
</tr>
</tbody>
</table>
6. Is the ratio between the cost and the health benefit favourable compared with other options for preventive reduction of the disease burden?

<table>
<thead>
<tr>
<th>Rota</th>
<th>Tbc (all children)</th>
<th>HSV-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost-effectiveness analysis by RIVM ongoing</td>
<td>No, because not sufficiently effective</td>
<td>Assessment not yet possible</td>
</tr>
</tbody>
</table>

7. Does provision of vaccination presently serve an urgent or potentially urgent public health need?

<table>
<thead>
<tr>
<th>Rota</th>
<th>Tbc (all children)</th>
<th>HSV-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment not yet possible</td>
<td>No, risk groups for tuberculosis are mainly asylum-seekers and migrants, who could not be reached by vaccinating resident children; in adults tuberculosis is mainly pulmonary, against which BCG is not very effective</td>
<td></td>
</tr>
</tbody>
</table>

**Recommendation**

In view of the potential health benefit, the Committee regards vaccination against rotavirus-induced diarrhoea as an important development; when results of cost-effectiveness analysis are available Health Council will then report on the desirability of inclusion in the NIP; the Committee recommends research into which virus serotypes circulate in the Netherlands.

The Committee advises against tuberculosis vaccination for the general population. Desirability of inclusion should be reviewed in the event of relevant developments, and certainly within 5 yrs.
<table>
<thead>
<tr>
<th>HepA</th>
<th>CMV</th>
<th>Pa (older people)</th>
<th>Smallpox</th>
</tr>
</thead>
<tbody>
<tr>
<td>No, it is unlikely that the incidence of hepatitis A in the Netherlands could be significantly reduced by universal vaccination; selective vaccination of children with parents from high-risk countries may be efficient</td>
<td>Assessment not yet possible</td>
<td>Not known, effectiveness not established</td>
<td>Not known, but in view of high frequency of adverse reactions probably unfavourable</td>
</tr>
<tr>
<td>No, hepatitis A is normally benign in young children; because of reduced hepatitis A virus infection rate in the general population, fewer and fewer people have natural acquired immunity; as a result adults in particular are at increased risk of symptomatic infection, but precise data on incidence of disease and complications lacking; incidence of infections probably cannot be reduced further by vaccination</td>
<td>Assessment not yet possible</td>
<td>No, the effectiveness of pneumococcal vaccination when used in addition to influenza vaccination has not been properly demonstrated</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Committee does not regard general childhood vaccination as an option; vaccination of children with at least one parent from a country where hepatitis A is prevalent may be desirable, however131; Committee recommends investigating the risk of infection-related complications and the cost-effectiveness of selective vaccination of children with at least one parent from a country where hepatitis A is prevalent; when the results of such studies are available, the Health Council can report on the desirability of universal vaccination and selective vaccination of a subpopulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gather further epidemiological data on disease burden, particularly in the western conurbation; subsequently review desirability of inclusion</td>
<td>Do not include at present; perform update of systematic review of effectiveness since 2003, then review the situation; investigate the effectiveness of a conjugated vaccine</td>
<td>Do not include in mainstream programme; use in an emergency if necessary</td>
<td></td>
</tr>
<tr>
<td>Vaccination against</td>
<td>HIV infection and AIDS</td>
<td>Gastrointestinal ulcers and stomach cancer triggered by Helicobacter pylori</td>
<td>Pelvic inflammatory disease attributable to Chlamydia trachomatis</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Recipients</td>
<td>All children</td>
<td>All children</td>
<td>All children</td>
</tr>
<tr>
<td>Vaccination schedule(s)</td>
<td>Information not yet available</td>
<td>Information not yet available</td>
<td>Information not yet available</td>
</tr>
</tbody>
</table>

**Background**

| Associated condition(s) | Opportunistic infections and malignant conditions | Chronic gastric membrane inflammation, often asymptomatic, sometimes with dyspepsia; in 15-20% chronic recidivist gastric and intestinal ulcers; in 1-2% ultimately leading to gastric adenocarcinoma | Inflammation of the uterus and/or urethra, often (to ¼) asymptomatic, otherwise accompanied by pain when passing water and (elevated) excretion (men and women), intermenstrual blood-loss (women); in 15-40% of women pelvic inflammatory disease (PID) and abdominal pain, extra-uterine pregnancy or infertility | Asymptomatic in 30-60% of women and 5% of men; pain when passing water and (elevated) excretion (men and women), intermenstrual blood-loss (women); complications: pelvic inflammatory disease (PID) and abdominal pain, extra-uterine pregnancy or infertility |

**Aim of vaccination**

| Prevention of infection, or prevention of complications (therapeutic vaccination) | Prevention of chronic gastritis, gastric ulcers and stomach cancer | Prevention of disease and complications (infertility, chronic abdominal pain and extra-uterine pregnancy) associated with Chlamydia trachomatis infection | Prevention of disease and complications (infertility, chronic abdominal pain and extra-uterine pregnancy) associated with gonorrhoea |

**Mechanism of communication**

| Sexual, blood-blood contact, mother-to-child | Salivary, direct oral contact? | Considerable genetic heterogeneity complicates vaccine development; vaccine made from urease with cholera toxin as adjuvant efficacious in animal experiments; according to IoM, vaccine could be developed within 7 yrs | Three problems complicate vaccine development: absence of good animal model; symptoms of Ct infection largely caused by the immunological response to infection – it will be hard to avoid such effects with vaccination; Ct cannot be genetically manipulated; vaccine not therefore expected before 2015 |

**Type of vaccine and stage of development (producer)**

| Vaccine development problematic because virus interferes with internal working of immune system; established methods have so far failed to produce a safe and effective vaccine; candidate vaccines based on attenuated living virus are the most promising, but there is a safety risk; attenuated living virus that depends on an external factor (e.g. doxycycline) is a possibility | Salivary, direct oral contact? | Considerable genetic heterogeneity complicates vaccine development; vaccine made from urease with cholera toxin as adjuvant efficacious in animal experiments; according to IoM, vaccine could be developed within 7 yrs | Vaccine possibly available by 2015 (IoM) |

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198 The future of the National Immunisation Programme: towards a programme for all age groups
<table>
<thead>
<tr>
<th>Hepatitis C</th>
<th>Group A haemolytic streptococi</th>
<th>Infection of unborn and neonates children with group B haemolytic streptococci</th>
<th>Lyme disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td>Information not yet available</td>
<td>All women planning a family</td>
<td>Information not yet available</td>
</tr>
<tr>
<td></td>
<td>Assessment not yet possible</td>
<td>Information not yet available</td>
<td>Three doses: 0, 1 and 12 mths</td>
</tr>
</tbody>
</table>

| Liver conditions, jaundice, in the long term possibly cirrhosis, liver failure and liver cancer | GAHS causes a wide range of problems, from uncomplicated laryngitis and skin infections to life-threatening pneumonia, sepsis, necrotising fasciitis and toxic shock syndrome; also acute rheumatism and glomerulonephritis | Sepsis, infections of soft tissues, urinary tract infection, pneumonia; can lead indirectly to premature birth; if child is infected during birth, can lead to sepsis, meningitis and residual problems | Characteristic symptom is erythema migrans (EM), a gradually extending skin rash around a tick bite site, indicating infection with *Borrelia burgdorferi*; if not treated with antibiotics, infection can be disseminated, leading to conditions of the nervous system, skin, joints and heart |
| Prevention of hepatitis C and complications (cirrhosis and cancer of the liver) | Information not yet available | Prevention of infection neonates | Prevention of Lyme disease |
| Blood-blood contact | Respiratory | Respiratory, mother-to-child | Tick bites |
| Genetic and antigen diversity makes vaccine development difficult; vaccine not expected before 2015 | Vaccine development difficult because of lack of understanding of immunology and pathogenesis of GAHS disease and cross-reactions between streptococcal antigens and human tissue (heart, kidneys, cartilage and basal ganglia); IoM (USA) estimates that development of a vaccine will require about 15 yrs | No vaccine yet available; IoM (USA) estimates that a conjugated polysaccharide vaccine could in principle be developed within 7 yrs | In 1998 a vaccine based on heavily purified recombinant surface antigen A (OspA) (LYMERix, GSK) was registered in the USA; this vaccine prevented transfer by infected ticks; withdrawn from the market in 2002 by the manufacturer |
Vaccination would interfere with a balance that has existed since an early stage of human evolution; effect of vaccination on the incidence of reflux oesophagitis and oesophageal cancer is therefore difficult to predict.

STDs such as gonorrhoea and Chlamydia trachomatis infection can facilitate HIV infection.

### Table 15c

<table>
<thead>
<tr>
<th>Specific problem description</th>
<th>HIV</th>
<th>Hp</th>
<th>Ct</th>
<th>Go</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination would interfere with a balance that has existed since an early stage of human evolution; effect of vaccination on the incidence of reflux oesophagitis and oesophageal cancer is therefore difficult to predict.</td>
<td></td>
<td></td>
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<td>STDs such as gonorrhoea and Chlamydia trachomatis infection can facilitate HIV infection.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Assessment

1. **Is the disease serious for individuals and does it affect many people?**
   - Yes, infection with HIV-1 is the cause of a great deal of morbidity and mortality worldwide.
   - Yes, infection with Helicobacter pylori contributes to approximately 2,000 cases of stomach cancer and 50,000 cases of gastrointestinal ulcers per year; the condition is relatively common in non-western ethnic minorities; the incidence has been falling in recent years.
   - Yes, infection with *Chlamydia trachomatis* (*Ct*) is a major cause of serious abdominal conditions and infertility in women; an estimated 60,000 infections per year.
   - Yes, gonorrhoea is a cause of serious abdominal conditions and infertility in women; roughly 10 reported cases per 100,000 per year, under-diagnosis and under-reporting at least 50%.

2. **Is the vaccine known to substantially reduce disease burden?**
   - Assessment not yet possible.
   - Assessment not yet possible.
   - Assessment not yet possible.
   - Assessment not yet possible.

3. **Do adverse reactions significantly detract from the health benefit attainable?**
   - Assessment not yet possible.
   - Assessment not yet possible.
   - Assessment not yet possible.
   - Assessment not yet possible.
<table>
<thead>
<tr>
<th>HepC</th>
<th>GAHS</th>
<th>GBHS</th>
<th>Lyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, hepatitis C is a cause of liver conditions and jaundice, possibly leading ultimately to cirrhosis, liver failure and liver cancer; the spread of infections is linked to particular risk factors; the incidence has fallen sharply since introduction of screening of blood for HCV</td>
<td>Assessment not yet possible; GAHS can cause serious and life-threatening conditions, but there are few data on the disease burden in the Dutch population, linked to laboratory surveillance</td>
<td>Yes, infection of expectant mothers with GBHS is a major cause of premature birth, and sepsis, meningitis and residual problems in neonates; Trijbels e.a. estimated incidence of GBHS-sepsis within 7 days of birth at 1.8 per 1 000 live births (0.54 confirmed and 1.3 probable) in 1997-1998 (after correction for underreporting); the corrected incidence of meningitis was put at 0.14 per 1 000; following introduction of preventive guidelines, incidence of confirmed sepsis fell to 0.36 per 1 000 in 1999-2001; case fatality rate did not change discernibly and was put at 7% for confirmed GBHS-sepsis (1997-2001); incidence of GBHS-meningitis also remained unchanged at 0.16 per 1 000 live births (1997-2001) broadly unchanged</td>
<td>No, although can Lyme disease can be very serious if untreated; prevention is closely linked to risk factors and risk regions; in 2005 there were an estimated 17 000 cases of erythema migrans and 435 hospital admissions for Lyme disease</td>
</tr>
<tr>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
</tr>
</tbody>
</table>

The US vaccine is 80% efficacious against Lyme disease; it is likely to be less effective in NL because of greater diversity of Borrelia species.

In the USA, doctors and patients suspect a link between vaccination and joint pain and swelling; planned research by Federal Drug Agency did not go ahead because manufacturer withdrew vaccine.
<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>Hp</th>
<th>Ct</th>
<th>Go</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Is the discomfort associated with each separate vaccination in reasonable proportion to the health benefit for the recipient and the population as a whole?</td>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
</tr>
<tr>
<td>5. Is the discomfort associated with the vaccination programme as a whole in reasonable proportion to the health benefit for the recipient and the population as a whole?</td>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
</tr>
<tr>
<td>6. Is the ratio between the cost and the health benefit favourable compared with other options for preventive reduction of the disease burden?</td>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
</tr>
</tbody>
</table>

7. Does provision of vaccination presently serve an urgent or potentially urgent public health need?

**Recommendation**

In view of the potential health benefit, the Committee regards the development of a vaccine as important for many countries including the Netherlands; the promotion of vaccine research is recommended; review in the event of relevant developments, and certainly within 2 to 3 yrs.

In view of the potential health benefit, the Committee regards the development of a vaccine as important, but one is not expected before 2015; review in the event of relevant developments, and certainly within 5 yrs.

In view of the potential health benefit, the Committee regards the development of a vaccine as important, but none is yet available; review in the event of relevant developments, and certainly within 5 yrs.
<table>
<thead>
<tr>
<th>HepC</th>
<th>GAHS</th>
<th>GBHS</th>
<th>Lyme</th>
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<tbody>
<tr>
<td>Assessment not yet possible</td>
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<td>Assessment not possible</td>
</tr>
<tr>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
<td>Assessment not yet possible</td>
<td>No, vaccination of the general population not recommended</td>
</tr>
</tbody>
</table>

- Universal vaccination is not recommended; review in the event of relevant developments, and certainly within 5 yrs
- The Committee recommends further study of the disease burden associated with GAHS infections, followed by a review
- The Committee recommends investigating the potential value of vaccination by modelling, followed by a review
- The Committee advises against vaccination against Lyme disease for the general population
The future of the National Immunisation Programme: towards a programme for all age groups