Universal vaccination against meningococcal serogroup C and pneumococcal disease
brief in eng
Universal vaccination against meningococcal serogroup C and pneumococcal disease

to:

The Minister of Health, Welfare and Sport

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In anticipation of general recommendations on the revision and possible expansion of the National Vaccination Programme (NVP), the Minister of Health, Welfare and Sport asked the Health Council to advise her on universal vaccination against group C meningococci. Until recently, meningococcus C was a relatively unimportant cause of meningococcal disease in the Netherlands, which manifests itself as meningitis (inflammation of the cerebral membrane) or sepsis (blood poisoning). The importance of meningococci serogroup C as a cause of meningococcal disease has recently increased sharply, however. In 1999, 2000 and 2001 (up to and including October) respectively there were 80, 105 and 222 recorded patients with this form of the disease, accounting for 14, 19 and 36 per cent of all patients with meningococcal disease. The other cases in the Netherlands are nearly all caused by group B meningococci.

Although polysaccharide vaccines for group A, C, W-135 and Y meningococci have been available for some while, these vaccines provide only temporary immunity and are not effective in young children. New protein conjugate vaccines do not have either of these disadvantages. A vaccine for meningococci B is not available as yet.

Over the next few years the NVP will have only limited scope for including new vaccinations; opting for one vaccination reduces the opportunities for including others. The Health Council has in this context therefore chosen to advise jointly on vaccination against meningococcal serogroup C and pneumococcal disease. Pneumococci are important pathogens, causing serious invasive disorders such as meningitis, sepsis and pneumonia (inflammation of the lungs); they also cause less severe but very common disorders, such as inflammation of the middle ear,
inflammation of the paranasal sinuses and bronchitis. A protein conjugate vaccine for these infections has recently become available for use in children. This vaccine affords protection against seven very common types of pneumococci, providing around 60 per cent coverage in the Netherlands.

The Health Council considers that the NVP should comprise a limited number of necessary, effective and safe vaccinations. Changes in the vaccination programme must not jeopardise public confidence in the programme or willingness to take part in it. Extra injections are generally needed to incorporate new vaccinations in the NVP, whereas various considerations support sticking to the current maximum of two injections per session.

Based on the general considerations for the inclusion of vaccinations in the NVP, vaccination against both meningococcal serogroup C and pneumococcal disease is, in the Council’s view, very important to public health. It currently seems unlikely that any vaccines for other conditions which deserve higher priority based on the same considerations will become available during the next five years.

The Council has considered various scenarios for universal vaccination against meningococcal serogroup C and pneumococcal disease. It has been guided by two principles, (a) the effects on public health and (b) optimum integration in the existing vaccination programme.

Until the beginning of 2005 vaccination against meningococci serogroup C and other pneumococci will only be possible using separate vaccines. Vaccination against both meningococcal serogroup C and pneumococcal disease has the greatest impact on public health if carried out at two, three and four months of age (scenario 1). DPTP and Hib vaccines are already being administered at those ages, however, and it would be unwise, as said before, to increase the number of injections to three or even four. In the course of 2002 or 2003 it will probably be possible to introduce a new vaccination combining DPTP and Hib.

To avoid overloading the NVP, the Council has examined the possibility of administering the vaccines at a later age than two, three and four months. In the case of meningococci serogroup C, vaccination at the age of five and six months (scenario 2) or shortly after reaching the age of one year (scenario 3) is a realistic alternative, since the incidence of this disease is relatively low in the first year. Since two injections and one injection respectively suffice for these two scenarios, vaccination would also be more efficient than in early infancy. Postponing vaccination until the age of five months or later is not an alternative in the case of pneumococci, as the incidence of pneumococcal disease is already high by a very young age.

To sum up, the advice is to introduce vaccination against meningococci serogroup C as quickly as possible, using two injections at five and six months of age. A single injection shortly after reaching the age of one would be an acceptable alternative.

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Since there is a second peak in the incidence of group C meningococcal disease among adolescents, the Committee recommends that a one-off catch-up programme be conducted for all children aged 18 and under. This would achieve the maximum effect from vaccination more quickly. The Council recommends introducing vaccination against pneumococci at the age of two, three and four months as soon as combined administration of DPTP and Hib vaccines is possible. A catch-up programme would not be necessary here, given the concentration of pneumococcal disease in the first few years of life.

A combined vaccine for meningococcal C and pneumococcal infections will probably be available in early 2005. If research shows this combined vaccine to be safe, effective and efficient it would make sense to start using it on young infants. The next step, on which work is already taking place, is to extend this combined vaccine to include components aimed at group B meningococci. The Council considers that developing a combined meningococci B/C – pneumococci vaccine is very important to public health.

In all the scenarios described above it is very important to monitor for any adverse effects, for one thing so as not to jeopardise public acceptance of the growing number of vaccinations incorporated in the NVP. It is also important to continue microbiological monitoring so as to detect at an early stage any increase in invasive disease caused by serogroups and serotypes not targeted by the vaccines. Clinical monitoring of cases of meningococcal and pneumococcal disease is also important.

These changes in the NVP would entail a considerable amount of preparatory work, in particular organising the logistics, educating the public, holding a tender procedure and producing the vaccine. Various changes in the programme for vaccination against meningococci and pneumococci (some of them temporary) will be necessary in the next few years, and the Council attaches particular importance to educating the public, since there is as yet no vaccine for meningococci B, the prime cause of meningococcal disease, and protection against pneumococci is also far from complete at present. The information provided to the public should give a clear idea of the reasons for and importance of the changes, what temporary solutions are likely to be put in place, and the eventual prospects of a combined vaccine for meningococcal and pneumococcal disease.
Chapter 1

The request for recommendations

On 27 August 2001 the Minister of Health, Welfare and Sport—having previously requested ‘general’ recommendations on the revision and possible expansion of the National Vaccination Programme (NVP)—asked the Health Council of the Netherlands to make urgent recommendations on universal vaccination against group C meningococci (*Neisseria meningitidis* serogroup C; see Annex A). The present recommendations on this universal vaccination anticipate the general NVP recommendations and have been drawn up by a committee of the Health Council (see Annex B).

The Committee considers that universal vaccination against meningococci serogroup C infections cannot be viewed in isolation from vaccination against infections induced by pneumococci (*Streptococcus pneumoniae*). Protein conjugate vaccines have recently become available for both disorders, and these are safe and more effective than the polysaccharide vaccines previously available that were unusable in the under-twos (GR80, GR82). Over the next few years the NVP will have only limited scope for including new vaccinations: opting for one vaccination reduces the opportunities for including others. The Committee has therefore decided to advise jointly on vaccination against meningococcal serogroup C and pneumococcal disease together. Vaccination of the elderly against pneumococci is not addressed in these recommendations; the Council will advise on this separately.
Chapter 2

Considerations for the inclusion of vaccinations in the NVP

2.1 Format of the current NVP

The National Vaccination Programme (NVP) was formulated in the period after 1957 (Bur98). It is administered by the paediatric health care departments of the home care organisations and the Area Health Authorities under the supervision of the vaccination agencies. The ages at which routine visits to the paediatric health care service take place and vaccinations are done are set out in the table.

2.2 Considerations for extending the NVP

The number of infectious diseases against which vaccination is possible is steadily increasing. In the past, vaccinations important to public health could be incorporated in the NVP without major problems, but one is increasingly coming up against the limits of the NVP. The number of injections that can be administered to a child in one session is limited, for example (see below). Although various vaccines have for years been combined in a single injection, such as DPTP and MMR, there are limits to the extent to which new vaccines can be added. Alternative forms of administration (nasal sprays, oral administration) would seem to be possible for certain vaccines and could help to reduce the stress on children, but not in the short term. Owing to the success of vaccination and the reduced incidence of diseases vaccinated against, the drawbacks of vaccination are coming more to the fore. The public is also increasingly asking critical questions about vaccination. The Committee therefore considers it necessary—now
that a quick decision is needed on vaccination against infections caused by meningococci serogroup C and pneumococci—to explain as clearly as possible the considerations for adding a new vaccination to the NVP at this juncture (Str00, Ver00, Zeij00). These will be elaborated by the Committee on the Revision and Possible Expansion of the National Vaccination Programme.

In the Committee’s view the NVP should comprise a limited set of necessary, effective and safe vaccinations. It must therefore be geared to potentially serious disorders; disorders that have generally been found to cause little discomfort have no priority. Since vaccinations are in principle given to healthy children, vaccines should meet very stringent efficacy and safety criteria. The stress on the children must be acceptable and kept to a minimum. A new vaccination must not be added to the programme without careful consideration of the impact on public health. The severity of the disorder should be assessed on the basis of data on the burden of disease and the

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**Table Ages for routine visits to the paediatric health care service and vaccinations under the current NVP**

<table>
<thead>
<tr>
<th>month</th>
<th>Vaccination</th>
<th>Year</th>
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<tr>
<td>1</td>
<td>DPTP1 + Hib1</td>
<td>2½</td>
</tr>
<tr>
<td>2</td>
<td>DPTP2 + Hib2*</td>
<td>3</td>
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<tr>
<td>3</td>
<td>DPTP3 + Hib3*</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>DPTP4 + Hib4*</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td></td>
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<tr>
<td>6</td>
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<td>9</td>
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<tr>
<td>11</td>
<td></td>
<td>18 - 24</td>
</tr>
<tr>
<td>14</td>
<td>MMR1</td>
<td></td>
</tr>
<tr>
<td>18 - 24</td>
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</tbody>
</table>

DPTP = diphtheria, pertussis, tetanus, poliomyelitis
MMR = measles, mumps, rubella (German measles)
Hib = Haemophilus influenzae type B
proportion of this that could be prevented by vaccination. Social factors are also important, e.g. the extent to which an epidemic could be controlled other than by vaccination under the NVP and the extent to which the disease can disrupt normal life. The cost-effectiveness of a new vaccine should be assessed and compared with that of other possible vaccines. Changes in the vaccination programme must not jeopardise public confidence in the programme or willingness to take part in it.

Extra injections will generally be necessary if new vaccinations are added to the NVP. The Committee has therefore paid special attention to the number of injections that can reasonably be administered to a child at one visit. Under the current NVP there are never more than two: this maximum has become established in practice and is not scientifically based. Nor is the Committee aware of any study, conducted in a setting comparable with the NVP, into the effect of the number of injections on acceptance. Although there is research that shows that parents are willing to accept additional vaccinations against meningitis (Paul00), this study did not examine whether they are willing to accept three injections at the same visit. Some of the criteria mentioned above provide grounds for sticking to a maximum of two injections per session. The stress on children must be minimised, and changes must not be at the expense of willingness to participate in the programme. The Committee has received indications from the people who administer the vaccinations, e.g. the National Centre for Parent and Child Care (LCOKZ), which suggest that introducing a third injection would meet with objections from a significant proportion of parents. There is experience of a third injection in children whose mothers turned out to be carrying the hepatitis B virus during pregnancy. Such children are usually vaccinated against hepatitis B when they receive the standard vaccinations against DPTP and Hib. In practice, after the shock and pain of the first two injections a third one leads to severe crying fits in a considerable proportion of the children, and sometimes to panic among their parents. Parents therefore often ask for a separate appointment for the hepatitis B vaccination. Simplicity and uniformity, which are partly responsible for the high level of acceptance of the current NVP, would evidently be reduced if a third injection were to be introduced. The experience of the people who administer the injections is that introducing three injections at a session also adversely affects other objectives of visiting the clinic, e.g. providing advice. The Committee is afraid that increasing the number of injections at one visit under current circumstances would lead to reduced acceptance and coverage of the NVP. The Committee would recommend introducing a programme of three injections at one session only if future research into the factors that determine acceptance supports this.
3.1 Meningococci serogroup C

Man is the only natural host for meningococcus (*Neisseria meningitidis*). Bacterial transmission occurs via direct contact or by what is known as ‘droplet infection’. By no means everyone infected becomes ill; people often become (temporary) carriers. Meningococci are classified into serogroups, including A, B, C, W-135, X, Y and Z. Groups B and, more recently, C are the main problem in the Netherlands. Until recently, only polysaccharide vaccines were available, for groups A, C, W-135 and Y, but these vaccines induce only short-term immunity and are ineffective in young children. New protein conjugate vaccines do not have either of these disadvantages. They are effective against all meningococci serogroup C strains as a rule, but not against group B meningococci.

The manifestations of meningococcal disease, which can be very severe and acute, include meningitis (inflammation of the cerebral membrane, around 85 per cent of cases) and sepsis (blood poisoning, 15 per cent of cases). The generalised blood clotting associated with meningococcal sepsis that can lead to shock, organ failure and loss of limb function is especially notorious. There is no clear difference between group B and group C in terms of the seriousness and outcome of meningococcal disease. In both cases, mortality averages ten per cent, but this percentage is much higher for sepsis (around 21 per cent) than for meningitis (eight per cent). About ten per cent of patients experience lasting residual disorders, such as neurological damage, amputation of limbs and scarring (Dan01, Deu00).
The number of patients with meningitis or sepsis as a result of infection by group C meningococci more than doubled in 2001, compared with previous years. In the period from January to October 2001 222 cases were recorded, while the number of cases of the disease since record-keeping began at the Netherlands Reference Laboratory for Bacterial Meningitis (NRBM) in 1959 used to fluctuate between 50 and 100 a year. The incidence is also higher than in an earlier epidemic increase in the early 1990s, when around 120 cases a year were recorded. The proportion of group C has also increased compared with other groups, in which no such increase is taking place. Until recently, meningococcus C was a relatively unimportant cause of meningococcal disease in the Netherlands: in 1999 it accounted for 14 per cent of cases (80/563). In 2000 the proportion of serogroup C cases rose to 19 per cent (105/539), and in the period January-October 2001 to 36 per cent (222/610). The cases not caused by group C are nearly all attributable to group B. Research shows that 20 to 30 per cent of cases of meningococcal disease are not reported to the NRBM; the numbers quoted have not been corrected for this (NRBM01, written communication, 2001).

The mean age for group C meningococcal disease was higher than for group B; this may indicate that a pathogen is involved against which the population has relatively little resistance, which thus also affects a relatively large number of older children and adults. Unlike group B meningococcal disease, the number of cases among children under the age of one was relatively small; as with group B, there are peaks in the ‘1-4 years’ and ‘15-19 years’ age groups.

Microbiological typing shows that the increase in group C meningococcal disease is caused by a limited number of subtypes. Most belong to the ET-37 complex; these bacterial isolates are associated with greater spread and virulence. Two clusters were identified in 2001: one on the island of Tholen (January-February 2001, four patients infected with an identical strain) and one in Zevenbergen-Klundert at the end of July 2001 (five patients infected with a different strain). In other parts of the country as well (Friesland-Groningen-Drenthe and Leiden) increased incidences of possibly related cases occurred in a short space of time.

A similar increase in the number of cases of group C meningococcal disease occurred earlier in e.g. Great Britain (starting in the early 1990s; Mil01) and Belgium (starting in 2000). In view of experience in neighbouring countries and the duration and extent of the current epidemic increase in the Netherlands, the Committee considers it unlikely that the incidence will return to the previous level in the short term.
3.2 Pneumococci

Man is again the only natural host for pneumococcus (*Streptococcus pneumoniae*). Here too the transmission of bacteria is via direct contact or by ‘droplet infection’, and by no means everyone infected becomes ill; people often become (temporary) carriers. Individual factors determine the occurrence of disease more than with meningococci. Pneumococci are important pathogens, causing serious invasive disorders such as meningitis, sepsis and pneumonia (inflammation of the lungs); they also cause less severe but very common, non-invasive disorders, such as inflammation of the middle ear, inflammation of the paranasal sinuses and bronchitis. On average, 11 per cent of patients with invasive disorders die from them. The outcome of pneumococcal meningitis is often much more serious than that of the meningococcal form of the disease, with a mortality rate of 15-20 per cent. Meningitis caused by pneumococci is also more likely to leave serious residual disorders, including hearing problems (15 per cent) and neurological abnormalities, such as mental retardation, spasticity and epilepsy (12 per cent) (Rüm01, Spa00). The mortality rate for invasive pneumococcal disease without meningitis is around six per cent.

About 90 different groups of pneumococci are known—called ‘serotypes’ in this case—and are found with widely differing incidences. Acquired resistance to pneumococci is predominantly type-specific. The protein conjugate vaccine that has recently become available—unlike the polysaccharide vaccine that has been available for much longer—is also effective in the under-twos (Bla00, Bla01, Esk01). It affords protection against seven very common serotypes, corresponding to at least 60 per cent coverage in the Netherlands. Vaccines with greater coverage will probably become available in the near future. By way of comparison, the ‘old’ polysaccharide vaccine is effective against 23 serotypes, though only in the over-twos and adults.

As regards the incidence of pneumococcal infections in the Netherlands, the NRBM has good information on meningitis. Between 200 and 250 cases of meningitis induced by pneumococci (around 80 in children aged 10 and younger) are recorded by the NRBM each year. Data on other forms of the disease is less reliable owing to considerable under-reporting (in the case of sepsis) or the absence of a specific reporting system (in the case of pneumonia and otitis media). Extrapolating from various research data, the Committee estimates 160 cases of sepsis, 7,500 cases of pneumonia and around 200,000 cases of acute otitis media (inflammation of the middle ear) per annum in the Netherlands in children aged 10 and younger (Bos JM, written communication, 2001). The incidence of pneumococcal disease has remained more or less constant in recent years, and is highly age-dependent; high-risk groups are children under the age of five and the over-65s. One major difference from
meningococci serogroup C is that pneumococcal disease does not usually occur in clusters, but spread out across the country.

### 3.3 Conclusion

Based on the considerations for the inclusion of vaccinations in the NVP (see 2.2), the Committee considers that vaccination against both meningococcal serogroup C and pneumococcal disease is very important to public health. Both bacteria cause serious disorders and a considerable burden of disease. Safe vaccines that are effective in infants have recently become available that could obviate much of this danger. In the case of meningococci serogroup C, the impact of the clustering on normal life is a further argument in favour of vaccination. It currently seems unlikely that any vaccines for other conditions which deserve higher priority based on the same considerations will become available during the next five years. In the next chapter the Committee describes various scenarios for including these two vaccinations in the NVP.
Chapter 4

Scenarios for universal vaccination against meningococcal serogroup C and pneumococcal disease

The Committee has considered various scenarios for universal vaccination against meningococcal serogroup C and pneumococcal disease. It has been guided by two principles: (a) the effects on public health, and (b) optimum integration in the existing vaccination programme.

The Committee would draw attention to a methodological aspect of health economics analysis that affects vaccinations. Both costs and effects on health are often discounted against a percentage reflecting expected economic growth. Discounting the effects on health has a major impact and severely disadvantages primary prevention programmes that have an effect only in the longer term. The Committee agrees with major commentators in the scientific press that there are important substantive grounds for adopting different discounting percentages in these cases for (a) costs and (b) health effects (Ble00, Hou98). The Committee therefore presents the estimates of cost-effectiveness both with and without discounting of the health effects. The scientific debate on this subject is still going on (Bar99, Gol96). The Committee on the Revision and Possible Expansion of the National Vaccination Programme will consider the debate in more detail in its general recommendations on the NVP. Under the current guidelines the financial costs and benefits are always discounted at the rate of four per cent.
4.1 Meningococci serogroup C

Protein conjugate vaccines for meningococci serogroup C are currently available from three manufacturers. These have proved extraordinarily effective in large-scale use in the United Kingdom, with a very low incidence of serious undesirable effects. From November 1999 infants are offered a routine 3 dose infant immunisation course, with a single catch-up dose for all children aged between 12 months and 17 years. A vaccine coverage of about 85 per cent in the targeted groups has resulted in a drop in the incidence of serogroup C disease of over 80 per cent. The frequency of adverse effects was similar to that after diphtheria and tetanus booster vaccination. The vast majority were non-serious reactions such as headache, local reaction, fever and dizziness. Serious adverse events were rare; for example, anaphylactoid reactions were reported at a rate of 1 per 500,000 doses distributed (Mil01).

**Vaccination at two, three and four months of age (scenario 1)**

To achieve the maximum health benefit and protect the youngest children against infection by meningococci serogroup C, vaccination should be carried out at two, three and four months of age, i.e. at the same time as the current DPTP and Hib vaccinations. Welte et al. at the National Institute of Public Health and the Environment (RIVM) have modelled the effects and costs of vaccination for the Committee (written communication, 2001).

The main factors, albeit uncertain, in the cost-effectiveness of vaccination are the expected incidence of group C meningococcal disease that would occur without vaccination, the duration of protection provided by vaccination and the cost of the vaccine. In the most plausible case these parameters have been set at 300 cases per year (corrected for under-reporting), 20 years and £15.88 per dose. The cost of administering the vaccine has been put at £5.22 per injection.

Vaccination could prevent around 22 deaths and 12 cases of severe residual disorders (neurological abnormalities and amputations) each year. These figures, however, are only achieved once equilibrium has been reached, after around twenty years of vaccinating infants. These are all cases that would have arisen in a particular year’s infants during the period that the vaccine affords protection, including at a later age, particularly during adolescence. Equilibrium could be achieved more quickly by performing a one-off catch-up vaccination of all children at a vulnerable age (up to around 18 years of age; see below).

The number of years of life saved is 1,485. A yardstick that also takes the effects on morbidity and residual disorders into account, and is therefore better suited to assessing vaccinations, is the QALY (quality adjusted life year). QALYs also make for
a better comparison with pneumococci. The expected benefit in terms of QALYs is 1,793 per year.

The net cost of vaccination would in this case be around €8.6 million (a gross cost of €12.3 million less a benefit of €3.7 million). The best estimate of cost per QALY is €17,600 (€4800 without discounting years of life gained).

In a sensitivity analysis taking account of the uncertainties in the principal parameters (incidence of disease caused by meningococci serogroup C: 150 cases per year; duration of protection: ten years; cost of vaccine: €11.34) the estimated costs varied between €12,400 and €66,100 per QALY (€3400 and €20,200 not discounted). The Committee concludes that the cost-effectiveness of vaccination against meningococci serogroup C infection is at a level usually considered acceptable for primary prevention programmes (Har01, Jan97, Ten95).

In countries where (conjugated) meningococci serogroup C vaccines have been investigated, inactivated polio vaccine (IPV) is generally not used. The registration file on the vaccines therefore does not extend to co-administration with IPV, which is included in the DPTP vaccine normally used in the Netherlands. It is conceivable, but not very likely, that the IPV and meningococci serogroup C vaccines could adversely affect one another. The Committee recommends that, if it is decided to vaccinate at the ages specified here, the data needed for registration in the Netherlands should be collected and analysed while using meningococci serogroup C vaccine in the NVP. Research of this kind is also going on in France and Germany, and the results are expected to become available during 2002.

**Vaccination at five and six months of age (scenario 2)**

Between January 2000 and July 2001 only a small proportion of cases of meningococcal serogroup C disease occurred in very young children. No cases were recorded up to four months of age, while two to three per cent of cases occurred in infants aged 4-6 months and five per cent in the under-ones. In the case of meningococcal serogroup C disease a high proportion of the health effects of vaccination could thus be achieved by vaccinating, perhaps temporarily, at later ages than those for the basic vaccinations against DPTP and Hib, namely two, three and four months. This is an important point, as there is currently little scope for adding new vaccines at these ages.

Unlike in the Netherlands, there have been cases in children under the age of four months in the United Kingdom. This is probably due to the fact that the epidemic increase there had been going on for a number of years before it was decided to vaccinate. The timely introduction of universal vaccination in the Netherlands might have the effect of limiting the spread to these very young children.
If immunisation is to be effective in very young children it has been found that more injections of the vaccine are required than in older infants and toddlers. According to the current registration files for vaccination under the age of one year, three injections at one-month intervals are needed. For children over the age of one, however, one injection is sufficient, owing to the growing maturity of the immune system: this is probably a gradual process. The United Kingdom now has ample experience of vaccination schemes involving the administration of two doses to the under-ones to protect against both meningococcal serogroup C and pneumococcal disease. Published research findings and unpublished research findings which the Committee has seen show that these two injections are sufficient; whether a booster after the age of one is useful or necessary is not yet clear (Mil01, Ric99, Ric01).

In view of the above considerations the Committee has also looked at a vaccination programme involving the administration of two doses at the ages of five and six months. As said before, postponing vaccination to these ages results in only a small reduction in effectiveness, amounting to two or three per cent of the total number of cases. Until recently all children used to pay routine visits to the paediatric health care service at these ages. Inquiries have revealed that routine visits at the age of five and six months are no longer universal. If it is decided to vaccinate at these ages, these visits should be incorporated in the standard service provided by the paediatric health care departments, which is currently under development. The government, the manufacturer and the Medicines Evaluation Board should also agree on use of the meningococci serogroup C vaccine in a two-dose regimen. The cost-effectiveness of vaccination at five and six months is intermediate between that of vaccination at two, three and four months (see above) and that of vaccination at 12-14 months (see below).

Vaccination at 12-14 months of age (scenario 3)

Vaccination at the age of 12-14 months would be more compatible with the structure of the current NVP than vaccination at five and six months, but it would not prevent so many cases of disease and mortality. The difference is estimated at a few deaths per annum, roughly five per cent of the total. Since vaccination at this age requires only one injection, it is much more cost-effective than vaccinating infants. Modelling has also been carried out for vaccination at 12 months. In the most likely scenario described above (300 cases per year, 20 years of protection and €15.88 per vaccine dose), vaccination at this age could prevent around 20 deaths and 10 cases of serious residual disorders each year. The net cost of the vaccination would be around €0.9 million (a gross cost of €4.1 million less a benefit—medical expenses avoided—of €3.2 million). The cost per QALY gained are around €2100 (€590 not discounted). Compared with the other scenarios, the changes in incidence, length of protection and cost of vaccine have relatively little impact on cost-effectiveness here.
The cost-effectiveness of vaccination at 14 months, at the same time as the MMR vaccination, is of the same order of magnitude. This would, however, limit the scope for a booster against pneumococci at that age (see 4.2), since this would necessitate giving three injections at one session if the same visit were to be used for the booster. The Committee would therefore favour vaccination against meningococci serogroup C at the age of 12 months in this scenario.

**Catch-up vaccinations**

Since there is a second peak, as said before, in the incidence of group C meningococcal disease among adolescents, it would be advisable to implement a one-off catch-up programme for all children aged 18 and younger. According to the registration files for meningococci serogroup C vaccines, three injections at one-month intervals are needed for children aged 2-12 months and a single dose for children over the age of one. Generally speaking, children should be called up separately for these vaccinations. Welte et al. have modelled the cost-effectiveness of catch-up vaccinations, but based on the assumption that only children older than 14 months would be vaccinated, resulting in some underestimation of both costs and benefits. 228 deaths and 92 cases of serious residual disorders (neurological abnormalities and amputations) could be avoided by a catch-up programme of this kind. In other words, the benefits of discounting are around 11,300 years of life gained or 13,500 QALYs. The costs of the catch-up programme are put at € 78.5 million, assuming € 135,000 for setting up the programme, a cost of vaccine of € 15.66 per dose and a cost of administering the vaccine of € 9.53 (call-up, consultation, etc.). The cost per QALY gained is € 11,800 with discounting and € 3600 without discounting. In the United Kingdom there are indications that a large-scale catch-up programme provides group immunity (Kaczmarski E, written communication, 2001). Since the model does not take account of group immunity, the actual cost-effectiveness of the catch-up vaccinations is probably greater than estimated here.

### 4.2 Pneumococci

One protein conjugate vaccine for pneumococci is now available. As stated at 3.2, it is effective in the under-twowos, affording protection against seven very common serotypes, thus providing around 60 per cent coverage in the Netherlands. Vaccination could prevent a relatively large proportion of the serious disorders caused by pneumococci (around 50 per cent of meningitis, 40 per cent of sepsis). It would prevent a much smaller proportion of the less serious disorders (around ten per cent of pneumonia, five or six per cent of acute otitis media). The incidence of serious undesirable effects is very low (Bla00, Bla01, Esk01).
More than in the case of meningococci serogroup C, the age-specific incidence of pneumococcal disease calls for vaccination at the earliest possible age. There is a strong concentration of pneumococcal disease in the first five years of life (and in the over-65s). Unlike with meningococci serogroup C, the incidence is also high during the first year of life, even the first months of life. Thus in the case of pneumococci there is no worthwhile alternative to vaccination at two, three and four months, at the same time as DPTP and Hib. A booster in the second year of life is recommended. As already mentioned in the discussion of vaccination against meningococci serogroup C, British research data indicates that two basic injections in the first year of life also suffice for pneumococci vaccination (Mil01, Ric99, Ric01). The current registration file for the only vaccine currently available for use in young children, however, prescribes three injections for children of six months and younger. Owing to the concentration of pneumococcal disease in the first few years of life, a catch-up programme is not necessary.

The Committee has compared the available—sometimes conflicting—research reports on the cost-effectiveness of pneumococcal vaccination (Bos00, Hvi01). Bos et al. then carried out computations with an improved model and made these available to the Committee (written communication, 2001). The main factors that determine the cost-effectiveness of vaccination are the cost of the vaccine and the extent to which indirect costs are taken into account, e.g. that of parents’ time off work. In the most plausible scenario the cost of vaccine has been set at £40 per dose and the duration of protection at ten years, with no indirect costs taken into account. A cost of £5.22 per injection has been calculated for administering the vaccine. Vaccination of infants could prevent around 11 deaths and 11 cases of serious permanent injury (neurological abnormalities, deafness) every year. In addition, just under 100 cases of meningitis or sepsis, 3200 cases of pneumonia and 36,000 cases of inflammation of the middle ear could be avoided. The computations do not take other positive effects of vaccination, on respiratory infections, into account (Dag01). In other words, around 900 years of life and 950 QALYs could be ‘gained’ each year. The net cost of vaccination is around £28.5 million per annum (a gross programme cost of £34.5 million less a benefit—medical expenses avoided—of £6.0 million). The cost is around £88,300 per QALY gained (£29,900 without discounting).

In an alternative scenario the cost of vaccine has been set at £15.88, as for the meningococci serogroup C vaccine. The cost of vaccination would then be £30,800 per QALY gained (£10,400 not discounted). In pneumococcal infections the indirect costs are, as said before, of great importance, but it is difficult to arrive at reliable estimates of these. Furthermore, only very limited data is available on the long-term consequences of infection. The lower limits of cost-effectiveness have been explored in sensitivity analyses by taking account of these factors. Including the available...
estimates of indirect costs in the model, using what is known as the ‘friction cost method’, and adopting less conservative estimates of long-term consequences have a positive impact on cost-effectiveness, as expected. The cost per QALY gained would then be €58,700 (€21,800 without discounting) with a cost of vaccine of €40, and €9100 (€3400) with a cost of vaccine of €15.88. The Committee concludes that the cost of vaccination against pneumococci at the current cost of vaccine (€40) is high, especially compared with other primary prevention programmes (Har01, Jan97, Ten95).

4.3 Conclusion

Vaccination against both meningococcal serogroup C and pneumococcal disease has the greatest effect on public health if done at two, three and four months of age (scenario 1). As the incidence of meningococcal serogroup C disease in the first year is relatively low, vaccination at five and six months (scenario 2) or shortly after reaching the age of one (scenario 3) is a realistic alternative, and the reduction in effectiveness would still be fairly small. Since two injections are sufficient at five and six months, or one injection at the age of one, vaccination would be more cost-effective at these ages than in early infancy. If universal vaccination is to be given against pneumococci, deferred vaccination is not an alternative: vaccination should be carried out in early infancy, since the incidence of pneumococcal disease is already high at this age.
Chapter 5

Recommendations

5.1 General recommendations on the National Vaccination Programme

The questions addressed in this report are part and parcel of a larger set of questions concerning the NVP. These questions, set out in a request for recommendations from the Minister of Health, Welfare and Sport (Annex A), concern the general desirability of including new vaccines in the NVP, the selection of particular vaccines and combinations of vaccines, the age at which the vaccines are to be administered, the expected side-effects, the assumptions to be adopted when calculating cost-effectiveness, the number of injections that can be given at one time in the light of public acceptance, the number of vaccinations that can be given in total in view of the way the immune system works, and the possibility and desirability of dropping certain elements of the current NVP. It has not been possible to deal exhaustively with all these questions within the scope of this report on vaccination against meningococcal serogroup C and pneumococcal disease. Nevertheless, the Committee has explicitly addressed a number of general questions in relation to these specific recommendations, e.g. the number of injections that can be given at one time in the light of public acceptance. The questions set out above will be examined in detail in the general recommendations, which will cover not only the questions mentioned but also the scientific aspects of informing the public and the possible impact of vaccination on the maturing of the immune system. On the strength of current scientific knowledge the Committee considers that the recommendations on meningococcal serogroup C and
pneumococcal disease are in line with the general ideas on vaccination under the NVP, some details of which have yet to be dealt with.

5.2 Vaccination in the period 2002-2005

The Committee considers that universal vaccination against both meningococcal serogroup C and pneumococcal disease is very important to public health and urges that both vaccinations be included in the NVP (Chapter 3). Until the beginning of 2005 vaccination against meningococcal serogroup C and pneumococcal disease will only be possible using separate vaccines. To maximise the preventive effect it would be best for both vaccinations to be carried out at two, three and four months (Chapter 4). DPTP and Hib vaccines are already being administered at those ages, however, and it would be unwise, in the Committee’s opinion, to increase the number of injections to three or even four (see 2.2). There would be scope for one new vaccine to be added once the current number of two injections is reduced to one through combined administration of DPTP and Hib, to which there are no longer any scientific obstacles. Combined DPTP/Hib vaccines are already used abroad and it seems likely that combined administration of DPTP and Hib will also be possible in the Netherlands in 2002, or at the latest by 2003.

As said in Chapter 4, there are important reasons for not deferring vaccination against pneumococci until after early infancy. Vaccination against meningococci serogroup C, on the other hand, could be done at five and six months or shortly after the age of one with a slight loss in effectiveness and an increase in cost-effectiveness. Both vaccinations could thus be included in the NVP, even in the period up to 2005.

Meningococci serogroup C

The Committee recommends that vaccination against meningococci serogroup C be introduced as soon as possible. It bases this recommendation on the estimated potential health benefit, the adverse impact of the clustering of cases of disease on normal life and the favourable cost-effectiveness. The Committee would favour administration at five and six months of age, but, as stated at 4.1, this would involve a departure from the current registration file for the available vaccines. One practical problem is the fact that paediatric health check ups are no longer routine at the ages of five and six months. The Committee considers administration at 12-14 months to be an acceptable alternative. For epidemiological reasons the Committee would favour vaccination against meningococci serogroup C at 12 months of age. More rapid inclusion in the NVP might be possible if this were to be administered at the same time as the vaccination against measles, mumps and rubella (MMR) at the age of 14 months, thus obviating the need for another visit. An extra visit would have to be arranged for a
booster against pneumococci, however (see below). As pointed out at 4.1, a one-off catch-up vaccination is needed for all children aged 18 and under.

The Committee has no preference for any of the three vaccines now available on the Dutch market. Introducing this vaccination would entail a considerable amount of preparatory work, in particular organising the logistics, educating the public, holding a tender procedure and producing the vaccine. Even if this were to be undertaken without delay, vaccination under the NVP would not be a realistic possibility before 1 September 2002.

**Pneumococci**

In the interests of public health the Committee recommends that vaccination against pneumococci be introduced at two, three and four months of age, as soon as combined administration of the DPTP and Hib vaccines becomes possible. As stated at 4.2, this may be the case by 2002. A booster should be administered in the second year of life. With the current cost of vaccine the cost of vaccination against pneumococci is high, especially compared with other primary prevention programmes (Har01, Jan97, Ten95).

If the vaccination is introduced, infants with one or both parents born in a country where hepatitis B is moderately or highly endemic will be in a special situation. The Health Council recently recommended vaccination against hepatitis B in infancy for this group, which nationally accounts for around 15 per cent of infants, using a combined hepatitis B/Hib vaccine (GR01). A combined DPTP/HepB/Hib vaccine which, unlike the DPTP/Hib vaccine mentioned, is already available on the Dutch market, should be used for this group.

### 5.3 Long-term prospects

A combined vaccine for meningococcal C and pneumococcal infections will probably be available in early 2005. If research shows this combined vaccine to be safe, effective and efficient it would make sense to start using it on young infants. This vaccine would target nine common types of pneumococci, thus covering around 65 per cent of pneumococcal disease in the Netherlands. As said before, the meningococci serogroup C component of this vaccine is effective against all group C meningococci as a rule, but not against group B. The next step, on which work is already taking place, is to extend this combined vaccine to include components aimed at group B. Since a great deal of meningococcal disease in the Netherlands is caused by group B meningococci, the Committee considers that developing a combined meningococci B/C — pneumococci vaccine is very important to public health, and this vaccine
should be incorporated in the NVP in due course if the findings of research into its safety and efficacy are positive.

5.4 Monitoring

In all the scenarios described above great importance should be attached to the monitoring of any adverse effects. The British research and monitoring programme, which considers the public health aspects, sets a good example (Bla01, Mil01).

One consideration here is public acceptance of the increasing number of vaccinations in the NVP. The Committee recommends that research be commissioned to identify the factors that determine the public’s willingness to accept vaccination. Given the imminent changes in the NVP, monitoring of the actual level of vaccination is increasingly important and should be stepped up. Only by linking these two aspects will it be possible to gain the required understanding of the attitudes and behaviour of parents and children with respect to vaccination.

It is also important to continue the microbiological monitoring already being carried out by the NRBM so as to detect at an early stage any increase in invasive disease caused by serogroups and serotypes not targeted by the vaccine. Although scarcely any evidence of this has been found for either meningoccci or pneumococci in the hitherto relatively short follow-up period (Bla01, Esk01, Mil01), this needs to be properly monitored, since the protection afforded by the vaccines to be used is only partial at present.

Clinical monitoring of cases of meningococcal and pneumococcal disease is also important, as has already been carried out e.g. for Hib by the Dutch Paediatric Surveillance Unit (NSCK).

5.5 Public education

Vaccination is a matter of free choice. If the NVP is to serve the public interest as well as individual interests, a high level of acceptance is essential. It is the government’s task to provide citizens with proper information on the importance of vaccination to public health, its importance to individuals, the stress on the person being vaccinated and any risks. The Committee attaches particular importance to public education, which merits more attention than it is actually being given right now.

When it comes to vaccination against meningococci and pneumococci, the importance of proper public education should be stressed even more. Various changes, some of them temporary, will need to be made to the programme over the next few years for these vaccinations. No vaccine for meningococcal serogroup B is available yet, and the coverage against pneumococci is currently far from complete. The
information provided to the public should give a clear idea of the reasons for and importance of the changes, what temporary solutions are likely to be put in place, and the eventual prospects of a combined vaccine for meningococcal and pneumococcal disease.
References


Hvi01 Hvidsten K, Nab H. A pharmacoeconomic evaluation of the seven-valent pneumococcal conjugate vaccine in the Netherlands. Aangeboden voor publicatie.


Ver00 Verweij M. Ethische uitgangspunten voor het collectieve vaccinatieprogramma. Inf Bull 2000; 11: 258-61.

References
Annexes
On 12 January 2000 the President of the Council received a request from the Minister of Health, Welfare and Sport to make recommendations on vaccination against meningitis. The Minister’s request was worded as follows (letter no. GZB/GZ 2.030.527):

The annual incidence of bacterial meningitis in the Netherlands is around 770 cases, based on isolation work performed by the Netherlands Reference Laboratory for Bacterial Meningitis. Just under 40 per cent of these cases concern children under the age of five. The most important pathogen here is meningococcus type B. In all, 500-600 cases of meningococcal disease occur every year, with serotype B accounting for the highest proportion, around 85 per cent. The disease can take a very serious turn: it is estimated that around 40 people die from it each year and about 50 suffer lasting damage.

The National Institute of Public Health and the Environment has informed me of the current situation regarding the development of a meningococci B vaccine. Research on this new vaccine is being conducted at the present time. Phase 2 field research in Great Britain shows that administration of four doses of the vaccine elicits a good immune response to all six strains used.

If the findings of all the follow-up trials are favourable, meningococci B vaccine could be included in the National Vaccination Programme in six years, as part of a cocktail of vaccines already in existence or new vaccines (pneumococci, meningococci type C, Hib) or otherwise.

In the light of the above, I would like to ask you to advise me on the following points, based on current scientific knowledge:
the desirability of incorporating meningococci B vaccine in the National Vaccination Programme, including a review of the cost-effectiveness analysis by the National Institute of Public Health and the Environment the scope for and desirability of doing this as part of a cocktail of vaccines for other meningitis pathogens, namely the conjugated vaccine that has now become available for meningococci type C, the Hib vaccine and the forthcoming conjugated vaccine for pneumococci
the desirability of including the conjugated vaccine for meningococci serogroup C and/or pneumococci in the NVP before the meningococci B vaccine can be incorporated in the programme.

The Minister’s questions form part of a larger set of questions concerning the revision and possible expansion of the National Vaccination Programme.

On 31 May 2000 the Minister asked the Health Council of the Netherlands to give priority to making recommendations on the desirability of universal vaccination against hepatitis B. In response to this the Council recommended on 20 February 2001 that a subpopulation of infants should be vaccinated against hepatitis B. An assessment of the vaccination of children aged 9-12 had to be postponed in the absence of key data.

September 2000 saw the publication of the report entitled ‘Towards a vaccination programme for the Netherlands in the 21st century’, in which the National Institute of Public Health and the Environment analysed relevant developments in the field of vaccines and vaccination between 2000 and 2020. It examined the burden of disease that could be obviated, the cost-effectiveness and the potential for incorporation in the National Vaccination Programme (NVP) for all the vaccines currently available or in the pipeline. With reference to that report the Minister of Health, Welfare and Sport asked the Health Council on 29 September 2000 for recommendations on the following points (letter no. GZB/GZ 2.108.780):
the desirability of incorporating new vaccines in the NVP
the selection of specific vaccines and combinations of vaccines, with specific reference to expected undesirable effects
the age at which the vaccines should be administered
the assumptions adopted by the National Institute of Public Health and the Environment in calculating the cost-effectiveness of the vaccines in question
the number of injections that can be given at one time in the light of public acceptance
the number of vaccinations that can be given in total in view of the way the immune system works
the possibility/desirability of dropping elements of the current NVP

On 2 July 2001 the Minister asked the Health Council to prioritise making recommendations on pneumococci and meningococcal vaccines as part of the process of advising on the NVP. The following text is quoted from the Minister’s letter (ref. GZB/GZ 2.193.615):
In my letter dated 29 September 2000 (ref. GZB/GZ 2.108.780) I asked the Health Council to provide me with phased advice on the report by the National Institute of Public Health and the Environment entitled ‘Towards a vaccination programme for the Netherlands in the 21st century’. Further to that request, I would ask you to prioritise making recommendations on pneumococci and meningococci vaccines.

This request is prompted by current developments in vaccines. The pneumococci vaccine is already available to parents outside the NVP. I therefore look forward to receiving recommendations on the desirability of inclusion in the NVP in the near future.

Developments concerning meningococci B vaccine also make it desirable to receive advice from the Health Council as soon as possible. The National Institute of Public Health and the Environment is currently developing a meningococci B vaccine. Advice from the Health Council on the introduction of this vaccine in the NVP is important for a number of strategic choices which the National Institute of Public Health and the Environment needs to make as part of the development process.

On 27 August 2001 the Minister of Health, Welfare and Sport asked the President of the Health Council, as part of oral consultation on the epidemic increase in meningococci serogroup C infections that was occurring in the Netherlands at that time, for recommendations on universal vaccination against this infection. In view of the urgency of the situation, the Minister asked for the recommendations to be made no later than 31 December 2001.
On 13 June 2001 the President of the Health Council set up the Committee on the Revision and Possible Expansion of of the National Vaccination Programme for a period of five years in order to answer current and future questions concerning the National Vaccination Programme. He established an expert working group on 18 September 2001 specifically to deal with the question of vaccination against meningococcal and pneumococcal infections. The Committee on the present matter consists of all the members of this working group and the members of the Committee on the Revision and Possible Expansion of of the NVP:

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