National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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Background information for the advice of the Health Council of the Netherlands on the vaccination schedule of the National Immunisation Programme

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Synopsis

Optimising the schedule of the National Immunisation Programme
Background information for the advice of the Health Council of the Netherlands on the vaccination schedule of the National Immunisation Programme

The National Immunisation Programme (NIP) protects against twelve diseases. In order to make a vaccination as effective as possible, it is important to vaccinate children at the ideal ages and frequencies. The Minister of Health asked the Health Council of the Netherlands for advice on the schedule of the NIP. He wants to know which improvements can be made. RIVM was asked to supply a background document with relevant information.

The RIVM has examined the NIP and determined the optimal vaccination schedule for each of the twelve diseases. The current schedule meets most requirements. There is room for improvement for a few diseases. Now it's the Health Council's turn to assess the various possibilities and advise the Minister of Health, who will thereupon take a decision.

According to RIVM, a schedule with one jab less for tetanus and polio will still confer adequate protection. The jabs against diphtheria, pertussis, tetanus, polio, hepatitis B and Hib should be spread out more over a longer period of time. For preschool children the jab against pertussis, now at four years of age, is better off being administered at the age of five or six years old. The jab will likely be more effective and have fewer side effects at that age. On the other hand, the jab against measles at nine years of age should be moved forward to 2-4 years old. However, a combination vaccine is used for vaccination against measles and mumps, and the jab against mumps is best postponed.

Several of the NIP vaccines are combination vaccines, which have the advantage of necessitating fewer injections. They can, however, also make it more difficult to decide to administer a component vaccine at another age. One ideal vaccination schedule may therefore not be possible.

Keywords: National Immunisation Programme, vaccination, schedule, optimalisation, combination vaccines, ideal

Publiekssamenvatting

Optimalisatie van het schema van het Rijksvaccinatieprogramma
Achtergrondinformatie voor het advies van de Gezondheidsraad
over het vaccinatieschema van het Rijksvaccinatieprogramma

Het Rijksvaccinatieprogramma (RVP) beschermt tegen twaalf ziekten. Om een vaccin zo goed mogelijk te laten werken, is het belangrijk om kinderen op de gewenste leeftijden en niet te vaak of te weinig te vaccineren. De minister van VWS heeft de Gezondheidsraad advies gevraagd over het vaccinatieschema van het Rijksvaccinatieprogramma. De minister wil weten of er verbeteringen in het vaccinatieschema mogelijk zijn. Het RIVM is gevraagd om de relevante informatie op een rij te zetten.

Het RIVM heeft daarom het vaccinatieschema tegen het licht gehouden en het optimale schema bepaald voor de twaalf ziekten. Het vaccinatieschema blijkt voor een groot deel op orde te zijn. Voor enkele ziekten zijn er verbeteringen mogelijk. Het is nu aan de Gezondheidsraad om de verschillende mogelijkheden te overwegen en de minister te adviseren. Op grond daarvan neemt de minister een besluit.

Een prik minder tegen tetanus en polio geeft volgens het RIVM nog steeds goede bescherming tegen deze ziekten. Daarnaast kunnen de prikken tegen difterie, kinkhoest, tetanus, polio, hepatitis B en Hib beter over een langere periode worden verspreid dan nu het geval is. Verder is het beter dat de prik van kleuters tegen kinkhoest op wat latere leeftijd wordt gegeven. Deze prik werkt hierdoor waarschijnlijk beter en heeft dan minder bijwerkingen. De prik op 9-jarige leeftijd tegen mazelen kan juist beter op jongere leeftijd worden gegeven. Alleen zitten de vaccins tegen mazelen en bof in één prik en kan de vaccinatie tegen bof juist beter later worden gegeven.

De vaccinaties tegen negen van de twaalf ziekten worden gecombineerd. Dit heeft als voordeel dat kinderen minder vaak hoeven te worden geprikt. Het maakt het wel lastiger om te besluiten om een onderdeel van een gecombineerde prik op een ander moment te geven. Eén ideaal vaccinatieschema bestaat daardoor niet.

Kernwoorden: Rijksvaccinatieprogramma, vaccinatie, vaccinatieschema, optimalisatie, combinatievaccins, ideaal

Content

Preface

The minister of health requested the Health Council of The Netherlands to write an evaluative advisory report on the whole of the National Immunisation Programme (NIP; Rijksvaccinatieprogramma (RVP)) with a focus on the general performance of the current programme and the appropriateness of its immunisation schedule. RIVM has been asked to provide a document with background information. This text is intended to provide the conceptual framework for that document as well as the requested information. In writing the document a broad and diverse group of vaccination experts of RIVM were involved.

1 Background: The national immunisation programme in The Netherlands

1.1 Current content

The National Immunisation Programme (NIP) currently provides vaccination against 12 vaccine-preventable diseases (VPDs), i.e. diphtheria, pertussis, tetanus, poliomyelitis, *Haemophilus influenzae* type b disease, measles, mumps, rubella, meningococcal ACWY disease, hepatitis B, pneumococcal disease (10 serotypes), and human papillomavirus (HPV) infection (Figure 1) [1].

Figure 1 NIP vaccination schedule
Source: http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals
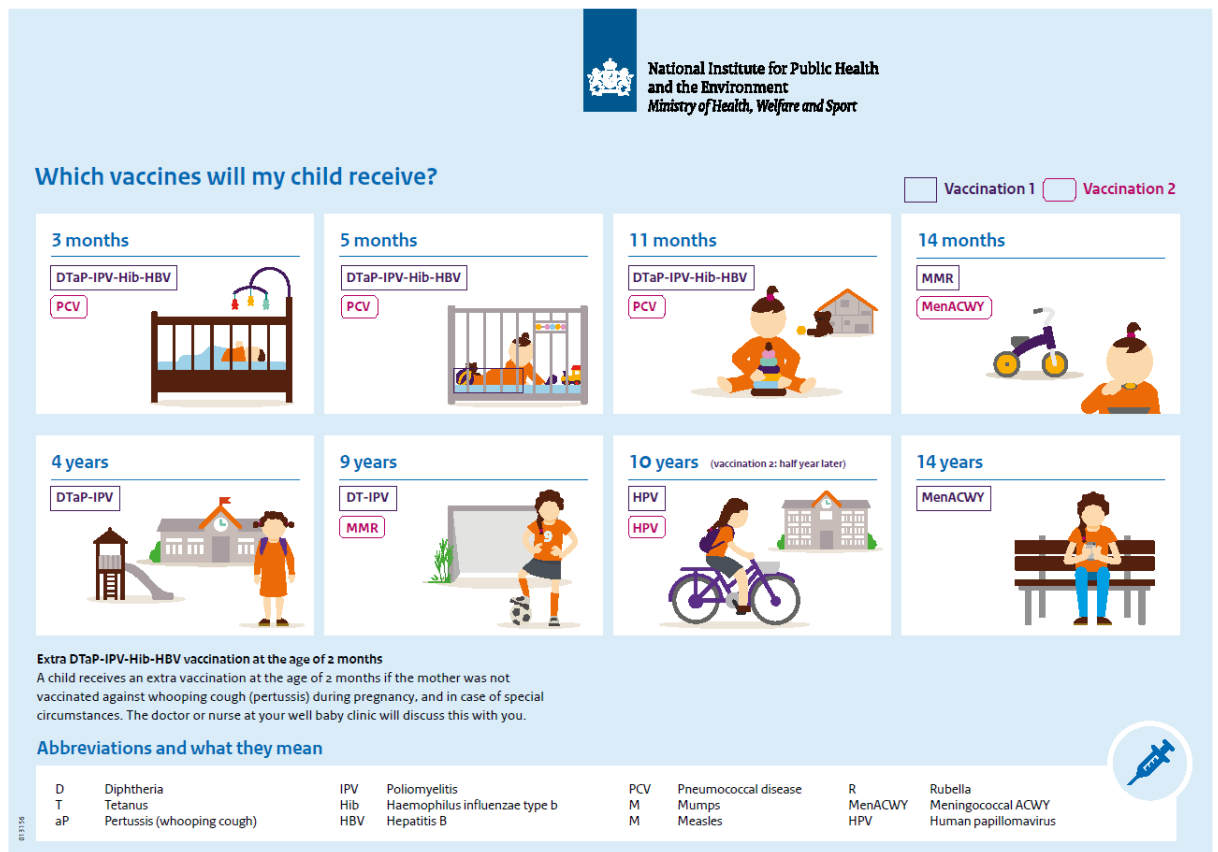
1.2 Primary objective[1]

The NIP is constantly developing. Against that background, it is important to ask what the programme's present objective is.

State intervention in vaccination and vaccination programmes is based on two principles. First, the government is tasked with protecting the population and the fabric of society. Secondly, it endeavours to achieve a fair distribution of care. Reasoning on the basis of these principles, the

[1] The second, third and fourth paragraphs of this chapter have been modelled from the 2007 and 2013 Health Council advisory reports 'The future of the National Immunisation Programme; towards a programme for all age groups'[2] and 'The individual, collective and public importance of vaccination.' [3].

Health Council of The Netherlands defined the objective of public vaccination programmes as:

Protecting the population of The Netherlands and the fabric of society against serious infectious diseases by means of vaccination

The provision of such protection is 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.

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 is inhibited. Thus, the national programme also benefits unvaccinated people and people who do not respond 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 everything is controllable. 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.

The principle of a fair distribution of care involves protecting those groups that are most urgently in need of protection. In the context of the NIP, achieving a fair distribution is not usually a problem. The NIP is mostly universal in nature, so it provides protection to everyone. Where vaccination targets specific subgroups, these are generally the ones that are in the most urgent need of vaccination. That is fair and, for specific diseases, it usually delivers the greatest health gains for the population. Nevertheless, the principle of a fair distribution of care – even in the context of the NIP – is certainly not irrelevant. For example, when assessing vaccination against cervical cancer in 2008, the accessibility (to all girls) of this important form of protection against a serious disorder, as well as the potential health gains at population level, were major factors behind the Health Council's recommendation that the vaccination should be included.

1.3 Three strategies

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

1. *To eliminate or eradicate serious infectious disease where possible.[2]*
2. *To reach and maintain herd immunity where possible.*
3. *To protect as many individuals in the vulnerable group(s) as possible (mostly defined by age only, sometimes also by sex and/or other characteristics).*

These three strategies provide a distinct hierarchy, where the first is the most and the third the least demanding strategy. Often, a public health vaccination starts as a programme following the third strategy, geared at protecting as many individuals in the vulnerable group(s) as possible. Whether or not herd immunity and elimination or even eradication are concrete possibilities will usually only become apparent over time.

The elimination or eradication of certain infectious diseases
Coordinated international action has succeeded in eradicating the dangerous disease of smallpox. So far, this remains a solitary success, however. The World Health Organization (WHO) has identified polio as an immediate target for eradication worldwide. For the WHO European region, diphtheria, measles and congenital rubella syndrome were identified as candidates for elimination in the next few years. The target for elimination of hepatitis B from the region was set for 2030.

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 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 immunity, the related condition may be eliminated without absolutely everyone being vaccinated. Where mumps, measles and rubella are concerned, for example, a vaccination coverage 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.

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[2] Elimination is the exclusion of a disease from a defined region. Following elimination, there remains a risk of reintroduction fromanother region. Eradication is the total exclusion of the relevant pathogen from the environment, so that it cannot return.

The protection of as many individuals as possible

If it is clear that herd immunity is an unobtainable goal – because, for example, vaccination uptake is low, or the vaccine-induced protection does not include transmission and/or is incomplete – the third subordinate objective may be adopted: to protect as many individuals as possible.

1.4 Target groups and criteria for inclusion of vaccinations

The 2007 Health Council advisory report 'The future of the National Immunisation Programme; towards a programme for all age groups' provides a framework for the selection of target groups for the public vaccination programmes as well as criteria for the systematic examination of arguments for and against the inclusion and prioritisation of particular vaccinations ('the seven criteria'). The framework was refined in their 2013 advisory report 'The individual, collective and public importance of vaccination'.

1. Is the protection adequate for all those intended to be protected?
The NIP was originally set up to tackle childhood diseases and thus children are the main target group of the programme. Within the framework of the current evaluation a major question is whether the NIP and its schedule is optimal for the protection of all individuals in the target groups? Examples of important issues in this respect are
   a. the protection of neonates and premature born children (in general);
   b. the protection of people who are immunocompromised;
   c. the protection of children born to mothers infected with a pathogen targeted by the NIP, such as the hepatitis B virus; and
   d. the protection of neonates and young infants too young to be vaccinated, such as against pertussis.

2 METHODS: The framework used for assessing the Immunisation schedule of the NIP

2.1 Assessment criteria (questions to be evaluated)

Assessment criteria for the immunisation schedule of the NIP were established to guide discussion of issues that could hamper reaching the goals of public vaccination and have implications for the immunisation schedule.

1. Is the protection adequate for all those intended to be protected?
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   a. the protection of neonates and premature born children (in general);
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   c. the protection of children born to mothers infected with a pathogen targeted by the NIP, such as the hepatitis B virus; and
   d. the protection of neonates and young infants too young to be vaccinated, such as against pertussis.

What could or should be done (more) to adequately protect these and other to-be-defined especially vulnerable subgroups?

2. Is the applied vaccination strategy optimal?
As indicated above, the strategies of the vaccinations of the NIP follow a defined hierarchy: first, to eradicate serious infectious disease where possible; second, to reach and maintain herd immunity, if possible; and third, to protect as many individuals as possible in the vulnerable group(s).

Whether or not eradication (or elimination) is a possible target, will usually be decided in an international context. Thus, The Netherlands will commit to the related international goals and targets. So far, only eradication of smallpox has been achieved, whereas eradication of poliomyelitis has come very close. WHO has designated poliomyelitis as an immediate target for eradication worldwide, diphtheria, measles and rubella as immediate targets for elimination from the WHO European region, and hepatitis B as a target for elimination from the WHO European region in 2030.

To reach and maintain herd immunity, when possible, greatly improves the effectiveness of vaccination programmes and thus the chances of elimination. If herd immunity is feasible, it should be an explicit goal of any vaccination programme. A clear example of herd immunity is vaccination against measles: if vaccination coverage in a population is above a threshold (about 95%) circulation of the virus becomes impossible and the disease disappears. For diseases where carriage of the microbium occurs, such as meningococcal and pneumococcal

disease, indirect protection is less clear-cut. For vaccination against disease caused by *Haemophilus influenzae* type b, complete herd immunity has not been reached and it is unclear whether it is feasible. For the current evaluation the important question is whether herd immunity is reached for all of the NIP vaccinations where it is feasible.

When herd immunity is not possible, the target should be to protect as many individuals as possible in the vulnerable group(s) and it should be ascertained whether this target is reached. A guiding example might be vaccination against cancer caused by human papilloma virus.

3. Does the programme include too much?
The NIP has grown and expanded over time. Additional jabs were added as deemed necessary. This raises the question whether the programme might have grown too big or too extensive. A possible example for discussion is provided by vaccination against tetanus. The WHO recommends three jabs in the first year of life for basis immunity and three booster doses thereafter for lifelong protection. In the NIP the number of tetanus toxoid containing immunisations is five for most participants and six for children of expectant mothers who did not receive the dtap jab during pregnancy as maternal protection against pertussis. The use of meningococcal and pneumococcal vaccines conjugated to tetanus toxoid may further affect the tetanus immune status. Similarly, for early protection against measles children receive MMR vaccinations at the age of 14 months as well as at the age of 9 years, whereas for protection against rubella one injection at school age might be sufficient. In the light of these and possible other examples it should be discussed whether the programme could or should be simplified and whether or not injections could or should be left out.

4. Does the programme include too little?
On the reverse side, to add an extra jab to the programme is a major decision which poses significant restraint. Therefore, it should also be discussed whether the programme does too little. Were jabs needed for adequate protection of the target groups inappropriately left out?

5. Is the timing of immunisations using combination vaccines optimal or at least acceptable?
Many immunisations come in combination vaccines. These provide important advantages in the number of jabs needed and the burden on participants of the programme. Combination vaccines, however, have drawbacks too. A component of a combination vaccine may negatively influence the efficacy of another component. More often, the various components of a combination vaccine may differ with respect to the most desirable timing of their administration. For example, the MMR combination vaccine is directed against such diverse situations as measles in young children, complications of mumps in adolescents and congenital rubella when vaccinated girls reach child-bearing age. Each of these situations would ask for a different timing of the combination vaccine. Is the timing of administration of combination vaccines right for the purpose of its various components? Are any compromises involved acceptable?

6. Are there important drawbacks of the NIP? For the population as a whole? For those who opt out? How are these drawbacks to be weighed against the advantages of the programme and its components?
Public vaccination programmes such as the NIP may have unforeseen effects limiting the overall positive result. It is good to keep an open eye for such drawbacks and weigh them against the advantages of the programme and its components. For example, after the introduction of vaccination against pneumococcal disease in the NIP disease caused by pneumococcal serotypes included in the vaccine have virtually disappeared, but other serotypes have been on the rise such that the net effect is smaller.
Undesirable effects may occur outside the programme, among people opting out. After introduction of general vaccination infection pressure may decrease and age at infection may rise, in some cases increasing the risks of infection, as was the case with mumps and rubella. How should such effects be valued?

2.2 Exploration of issues against the background of available knowledge

Each vaccination (pathogen) considered separately, at first
In the following section of this document, for each constituent vaccination of the NIP separately first a short history of its use is given, its current goal(s) are specified, and the epidemiology of the disease against which it is directed are specified. Secondly, the general assessment criteria outlined above are applied and issues specific for the vaccination are identified. Thirdly, these issues are explored against the background of available evidence. Finally, conclusions and suggestions for the request for advice from the Health Council are specified.
Thus, for each vaccination the following items will be detailed:
1. History of use;
2. Goal(s) as currently defined on the basis of Health Council advice;
3. Epidemiology of the targeted disease in The Netherlands;
4. Assessment of the vaccination against the six criteria, issues identified;
5. Exploration of the issues against the background of available knowledge

Optimal immunisation schedules and pragmatic compromise
Issues transcending the bounds of specific vaccinations and issues relating to the use of combination vaccines are considered later, in the fourth section of the document (General Discussion). In that section, too, the optimal immunisation schedules for each constituent vaccination separately are specified and potential conflicting considerations between these, most notably within combination vaccines, are highlighted for discussion in the Health Council.

2.2.1 *References*
1. The National Immunisation Programme in The Netherlands: surveillance and developments in 2019-2020. RIVM report 2020-0077. Bilthoven: National Institute for Public Health and the Environment, 2021.

2. The future of the National Immunisation Programme: towards a programme for all ages. Advisory report 2007/02E. Den Haag: Health Council of The Netherlands, 2007.
3. The individual, collective and public importance of vaccination. Advisory report 2013/21E. Den Haag: Health Council of The Netherlands, 2013.

3 Issues for specific vaccinations

3.1 Diphtheria

3.1.1 History of vaccination against diphtheria
Diphtheria toxoid vaccinations have been used in large-scale programmes in the Netherlands since 1952, with all cohorts born since 1945 invited. Vaccination against diphtheria is part of the NIP from 1957 onwards. In the current Dutch NIP, infants and children receive five or six diphtheria containing vaccinations, depending whether the mother received a maternal dtap vaccination during pregnancy. In this NIP schedule, diphtheria is part of a hexavalent DTaP-IPV-Hib-HepB vaccine for infants (3 or 4 doses), a dtap-IPV booster dose for 4-year-olds and a dt-IPV booster dose at 9 years of age. Furthermore, diphtheria toxoid is the carrier protein of one pneumococcal serotype in the 10-valent conjugated pneumococcal vaccine, currently administered in the NIP at 3, 5 and 11 months of age. From late 2019 onwards, diphtheria is also administered through the Tdap vaccination, advised to all pregnant women of 22w of gestation or more.

3.1.2 Goal of vaccination against diphtheria
The main goal of vaccination against diphtheria is lifelong prevention of all diphtheria disease, because diphtheria can lead to death or severe disease requiring hospitalization.

3.1.3 Epidemiology of diphtheria in The Netherlands
In The Netherlands, the yearly number of diphtheria cases remained below 5 from 2000 onwards, with no deaths reported (figure 1). All cases occurred in adults and the majority concerned cutaneous diphtheria. Some of these cases were in vaccinated people. Vaccination with diphtheria toxoid-containing vaccine might not prevent cutaneous colonization or infection with *C. diphtheriae* (1)*. The majority of diphtheria cases were contracted during traveling.
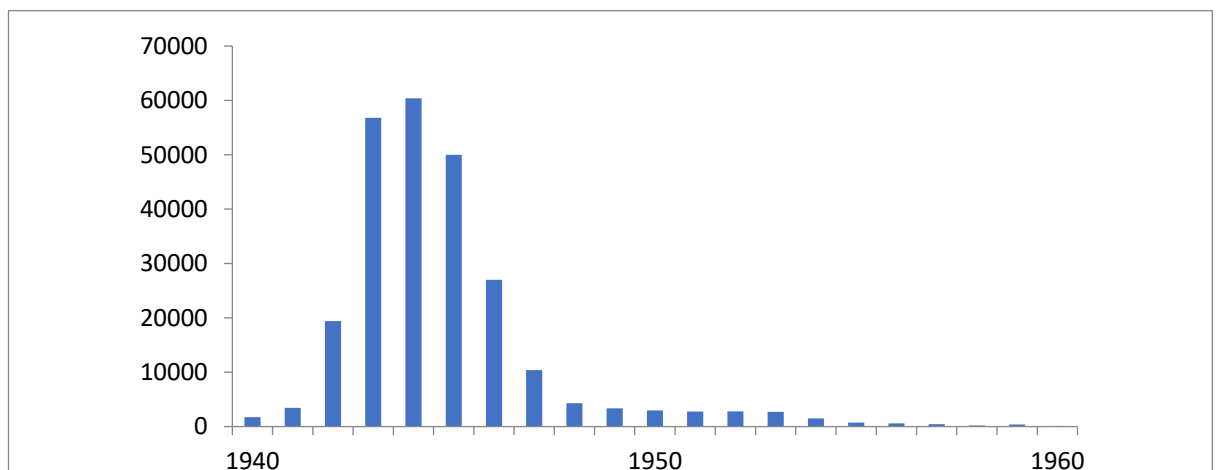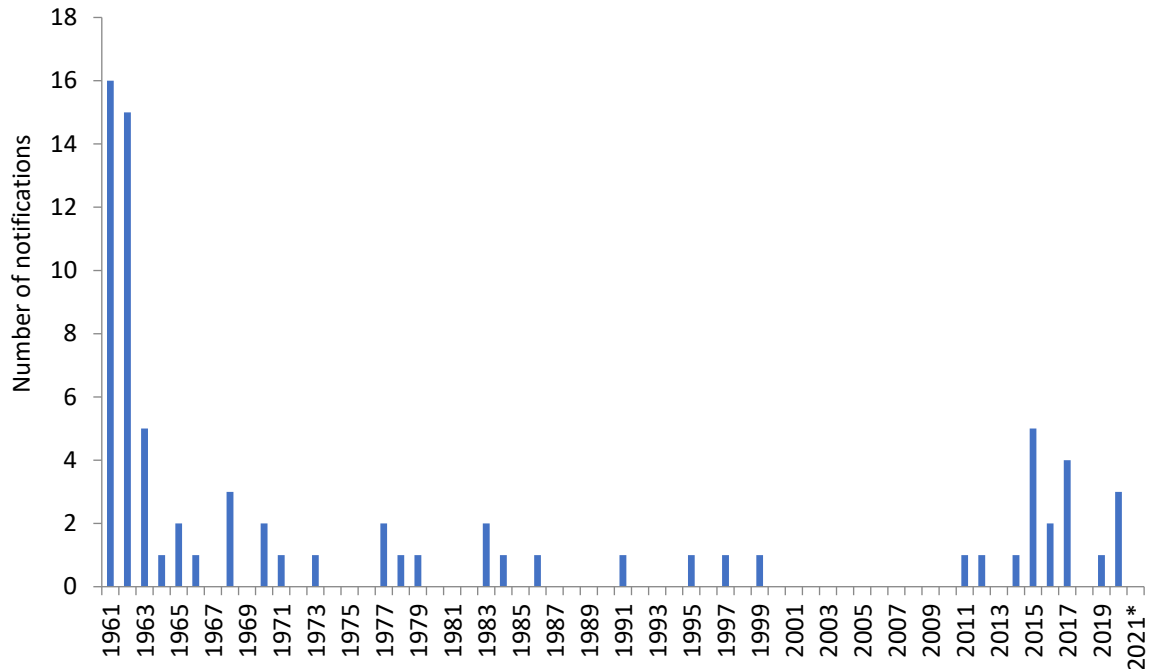
Figure 1 Diphtheria notifications per year for 1940-1960 (top part) and 1961-2021*(bottom part)
*notifications up to and including March 2021 are included

3.1.4   *Assessment of the vaccination against the six criteria, issues identified*
Criterion 1. Is the protection adequate for all those intended to be protected?
Immunosurveillance shows high or moderate seroprevalence, depending on the used cut-off for protection, i.e. 0.01 IU/mL (basic protection) or 0.1 IU/mL (more robust, long term protection). For orthodox protestants, the seroprevalence is much lower. Furthermore, anti-diphtheria antibodies in the national sample decline with age.

Issues related to criterion 1
- Anti-diphtheria antibody levels in the general Dutch population are declining during adulthood.
- The protection of orthodox protestant people that reject vaccination, is low.
- It is uncertain which cut-off for protection should be used to assess antibody levels in the population.
- The influence of cellular immunity is unclear.

Criterion 2. Is the applied vaccination strategy optimal?
From the start of the NIP, vaccination coverage of vaccines targeting diphtheria are continually high in The Netherlands. The number of diphtheria notifications ranges between 0 and 5 cases each year since 2000. From 2000 onwards, no diphtheria related deaths were reported. These surveillance data suggest that the applied vaccination strategy against diphtheria works well despite declining antibody levels in adults.

Criterion 3. Does the programme include too much?
The current NIP includes 5 or 6 diphtheria containing vaccinations, that are able to elicit a primary or booster immune response. Furthermore,

the implemented Tdap vaccination during pregnancy is also a booster dose in previously vaccinated women, with 70% vaccination coverage. Conjugate vaccines that contain diphtheria toxoid or diphtheria toxin cross-reactive materials (CRM) as a protein carrier, used e.g. for vaccination against pneumococcal and meningococcal disease, may also induce a booster response to diphtheria in persons previously immunized against diphtheria. In the current NIP, the 10-valent pneumococcal conjugate vaccine has one serotype that is conjugated toa diphtheria related carrier protein and is administered simultaneously with the infant hexavalent DTaP-IPV-Hib-HepB. The impact of this simultaneous administration on the overall anti-diphtheria antibody concentration is unknown. Due to the need of regular tender procedures for NIP vaccines, this might change, when a pneumococcal with different composition and vaccination schedule will be selected.

WHO recommends booster doses every ten years after a completed primary series throughout life. According to this WHO advice, the number of booster doses within the NIP (i.e. 3 doses at 11m, 4y and 9y of age) is more than advised for the period up to 18 years of age and less than advised for adulthood. At the same time, WHO states that seroprevalence data do not support the need for a decennial booster and thus less booster doses may be necessary.

Issues related to criterion 3
- What is the impact of diphtheria toxoid as a carrier protein in conjugated vaccines? Should elicited immune responses due to diphtheria related carrier proteins be counted as booster doses? What are possible consequences?
- The number of NIP booster doses could be lowered or spread out over the entire NIP age band (0-18 year).
- The maximal/optimal interval of booster doses at adult age is uncertain.

Criterion 4. Does the programme include too little?
No, there is no evidence that the programme has insufficient impact.

Criterion 5. Is the timing of immunisations using combination vaccines optimal or at least acceptable?
The primary series in the Dutch NIP include 2 or 3 doses, depending whether the mother received a Tdap vaccination during pregnancy. Doses at 11 months and 4 and 9 years are considered booster doses. For long-term and persisting protection against diphtheria in all age groups, WHO recommends booster doses every ten years after a completed primary series throughout life. This advice and seroprevalence data suggest that the interval between the diphtheria containing booster doses within the NIP can be extended.

Issues in relation to criterion 5
- Increasing the interval between diphtheria booster doses could prolong protection against diphtheria.

Criterion 6. Are there important drawbacks of the NIP? For the population as a whole? For those who opt out? How are these drawbacks

to be weighed against the advantage of the programme and its components?

No important drawbacks in relation to the public vaccination programme against diphtheria are known.

3.1.5   *Exploration of the issues against available evidence*
The anti-diphtheria antibody levels in the general Dutch population is declining during adulthood
Results of the second Pienter seroprevalence study (2006-2007) show that 9.4% of the national sample had anti-diphtheria antibodies < 0.01 IU/mL (2). Using the more robust 0.1 IU/mL level of protection, resulted in 46.3% unprotected people of the NS.

In relation to a European diphtheria seroprevalence study among 40-60-year-olds, with samples derived between 2015 and 2018, Pienter 3 (2016-2017) samples from this age group were analyzed (3). The percentage of unprotected 40-60-year-olds in The Netherlands, was 12.8% (<0.01 IU/mL) and 57.5% (<0.1 IU/mL).

Using a linear regression analysis among fully immunized individuals (i.e. six vaccinations up to 9 years of age) without evidence of revaccination, the Pienter 2 serosurveillance data also showed a continuous decline in antibodies (figure 2). However, geometric mean antibodies remained well above 0.01 IU/mL up to 40 years of age but already in 20-24 year-olds, a GMC below 0.1 IU/mL is reached.
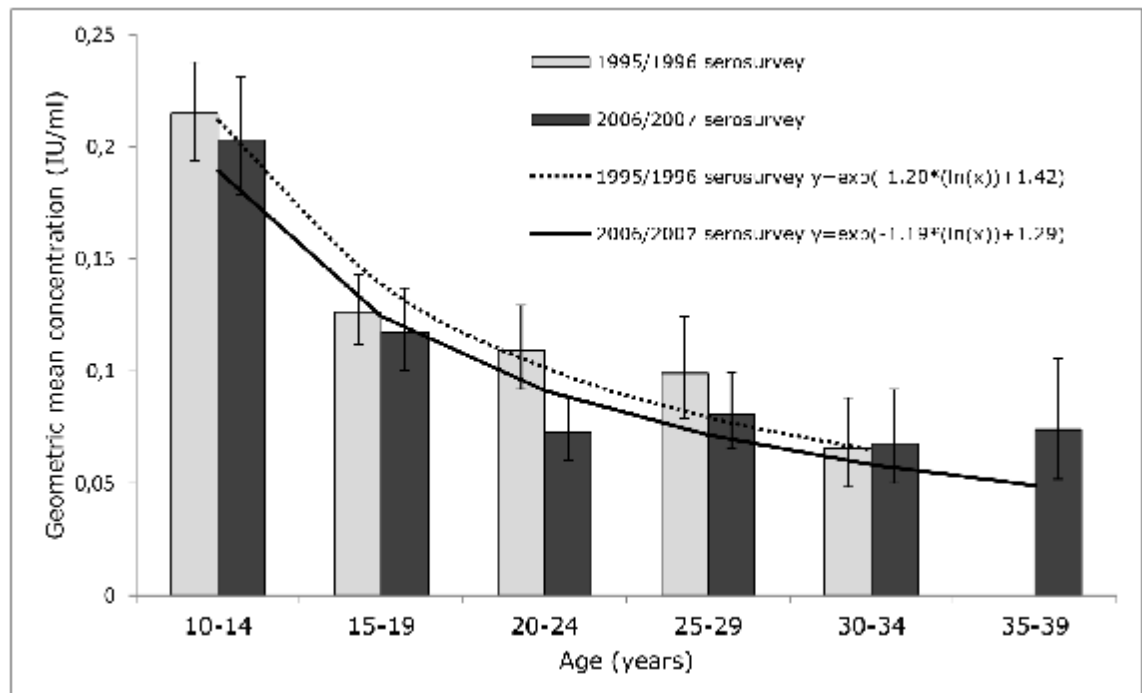

Figure 2 Persistence of diphtheria IgG antibody in 10-39 year old individuals, in the national sample of the 1995/1996 serosurvey (n=961) and 2006/2007 serosurvey (n=971), who were completely immunized against diphtheria according to the NIP, without evidence of revaccination.

The protection of orthodox protestant people is low
In the Pienter 2 seroprevalence study, 53.7% and 78.9% of the orthodox protestants had antibody concentrations < 0.01 IU/mL and < 0.1 IU/mL, respectively (2). Orthodox protestants often refuse vaccination on religious grounds. It is a well-known fact that the Netherland includes a groups of socio-geographically clustered people who refuse vaccination on religious grounds. This group comprises approximately 220,000 members (i.e. 1.3% of the Dutch population; reference date 1-1-2006) (4). About three quarter live in a municipality within the so called 'Bible Belt'. Almost a quarter of the orthodox protestants is living outside this area.

A study on the evolution of the vaccination coverage in this group shows that the coverage increases in subsequent generations with approximately 15% (5). The decision to vaccinate or not is mainly based on religious arguments, not on medical grounds (6).

Several other groups are also prone to have a lower vaccination coverage, e.g. people with a migration background or lower socio economic status (7). This is a problem in large cities, which needs special attention.

Which cut-off for protection should be used to assess the seroprevalence and what is the influence of cellular immunity?
Two cut-off's for seroprotection, i.e. 0.01 IU/mL and 0.1 IU/mL, are in place, which are both used to assess the seroprevalence in The Netherlands. Hereby, an antitoxin level of 0.01 IU/mL is the lowest level providing some degree of protection, and 0.1 IU/mL is considered a protective level of circulating antitoxin (8). The higher the antibody concentration, the milder the symptoms of diphtheria. However, sufficient circulating antibodies do not confer absolute protection.

In countries with longstanding childhood immunisation programmes, adults who have neither been exposed to diphtheria nor received booster doses of diphtheria toxoid may become susceptible to diphtheria as a result of waning immunity (8). During the outbreak in the former Soviet Union, waning of immunity was thought to contribute to the high incidence rate observed among adults (8) (9).

Vaccination also induces for both T-cells and memory B-cells. However, data on the magnitude of this influence is unknown.

What is the impact of diphtheria related carrier proteins in conjugated vaccines? Should elicited immune responses due to diphtheria related carrier proteins be counted as booster doses? What are possible consequences?
Conjugated vaccines are developed because children do not elicit an immune response to polysaccharide vaccines (10). After introduction of conjugated vaccines targeting *Haemophilus influenzae* type b, pneumococcal disease and meningococcal disease, also infants can be protected against these diseases. Tetanus toxoid, diphtheria toxoid or CRM197 (a genetically detoxified form of diphtheria toxin) are often used as a carrier protein. These carrier proteins also elicits a good immune response in children primed with TT or diphtheria vaccination

and can act as a boosting dose (11-13). From a regulatory perspective, the booster immune response of carrier proteins is not taken into account for licensing the vaccine (personal communication Bettie Voordouw). Furthermore the type of carrier protein can change if a new European tender procedure results in a change of a specific vaccine. Such a change can lead to a changing number of booster doses, if the immune response to the carrier protein is counted as an official booster dose. Yet, the use of conjugated vaccines may be associated with booster effects of antibodies against the carrier protein. Most likely these effects will be positive, i.e. reinforcing the effect of vaccination. However, negative effects due to interference might also be conceived.

Could the number of booster doses be lowered or the interval between doses be widened?
The current number of booster doses within the NIP is higher than advised by WHO. However, booster doses later in childhood are important to maintain high antibody levels during school-age years (8). In the Soviet Union, the immunisation schedule was changed in 1986, delaying the 6 year booster dose to age 9 years (8, 9). After the dissolution of the Soviet Union (1988-1991), a large diphtheria outbreak occurred in the newly independent states in the 1990s due to a large population of susceptible adults and decreased childhood vaccinations. Data showed that receipt of the booster dose at 6 to 8 years of age was found to decrease the risk of diphtheria in this age group.

The optimal interval between booster doses at adult age is uncertain
Booster doses during adulthood are necessary to maintain sufficient antibody levels for protection throughout life, because protection mainly depends on humoral response (8). Vaccination also induces cellular immunity for both T-cells and memory B-cells. However, data on the magnitude of this influence is not available.

The risk analysis, performed in the Pienter 2 seroprevalence study, revealed that an increasing interval between the last diphtheria containing vaccination and sampling, was associated with an increased risk of having antibody titres below 0.01 IU/mL (Table 1) (2).

The frequency of booster doses is point for discussion. Diphtheria toxoid is mainly administered in combination vaccines at least also containing tetanus toxoid. The frequency and timing of booster doses must be chosen carefully. In general diphtheria antitoxin antibody levels decline more rapidly than tetanus antitoxin antibody levels (8). Although rare, severe disease and even death due to diphtheria can occur in unvaccinated people (14, 15).

A randomized trial studying the immunogenicity of 2 diphtheria toxoid containing booster doses with 10 years interval, showed that >98% of participants still had seroprotective (i.e. ≥0.1 IU/mL) antibodies before administration of the 2nd dose (16). Similar results were seen in a Canadian study with >85% seroprotection rates before a decennial booster (17). These results underline the possibility of widening the interval of booster doses.

Table 1 Potential risk factors for having diphtheria antibody levels below 0.01
IU/mL in the national sample of the 2006-2007 serosurvey (n=6383).

Potential risk factor	n (%)	Crude OR (95% CI)[a]	Adjusted OR (95% CI)
Age group			
0 – 4	860 (13.5)	Ref	Ref
5 – 9	620 (9.7)	0.5 (0.3-0.9)	0.4 (0.3-0.8)
10 – 29	1441 (22.6)	0.6 (0.4-0.9)	0.3 (0.1-0.5)
30 – 49	1356 (21.2)	1.1 (0.8-1.6)	0.2 (0.1-0.4)
50 – 64	1130 (17.7)	2.4 (1.7-3.3)	0.3 (0.2-0.6)
65 – 79	976 (15.3)	4.1 (3.0-5.7)	0.5 (0.3-0.8)
Sex			
Male	2911 (45.6)	Ref	Ref
Female	3472 (54.4)	1.7 (1.4-2.0)	1.5 (1.3-1.8)
Religion			
Non-orthodox Protestant	6250 (97.9)	Ref	Ref
Orthodox Protestant	133 (2.1)	2.9 (1.8-4.6)	2.2 (1.3-3.5)
Educational level			
High	2401 (37.6)	Ref	Ref
Middle	3137 (49.2)	1.5 (1.2-1.8)	1.3 (1.0-1.6)
Low	730 (11.4)	1.4 (1.1-1.9)	0.9 (0.7-1.3)
Unknown	115 (1.8)	2.6 (1.5-4.6)	2.0 (1.1-3.6)
Years since last diphtheria vaccination			
0 (<12 months)			
1 – 4	856 (13.4)	Ref	Ref
5 – 9	1615 (25.3)	1.7 (1.0-2.8)	1.9 (1.1-3.1)
10 – 14	728 (11.4)	2.7 (1.4-5.1)	2.8 (1.4-5.3)
15 – 19	483 (7.6)	4.8 (2.5-9.1)	4.5 (2.4-8.7)
≥ 20	297 (4.7)	6.1 (3.1-12.0)	4.8 (2.4-9.5)
Not vaccinated	1836 (28.8)	9.2 (5.3-16.0)	5.7 (3.3-10.1)
	568 (8.9)	17.8 (10.3-30.9)	8.9 (5.0-15.8)
Number of registered diphtheria containing vaccinations			
6			
2-mei	1578 (24.7)	Ref	Ref
≥ 7	1959 (30.7)	0.6 (0.4-1.0)	0.8 (0.5-1.3)
0-1	358 (5.6)	0.2 (0.1-0.7)	0.4 (0.1-1.0)
	2488 (39.0)	3.3 (2.3-4.7)	2.7 (1.9-3.9)
Reported travel to high-risk regions			
Yes	2430 (38.1)	Ref	Ref
No	3850 (60.3)	2.1 (1.7-2.5)	1.3 (1.1-1.7)
Unknown	103 (1.6)	2.0 (1.1-3.7)	1.0 (0.5-1.9)
Reported revaccination because of profession			
Yes			
No	1077 (16.9)	Ref	
Unknown	3248 (50.9)	1.5 (1.2-1.9)	
	2058 (32.2)	1.2 (0.8-1.8)	

Potential risk factor	n (%)	Crude OR (95% CI)a	Adjusted OR (95% CI)
Ethnicity			
Dutch	4870 (76.3)	Ref	
First generation other Western	153 (2.4)	1.7 (1.1-2.7)	
Second generation other Western	292 (4.6)	0.8 (0.5-1.2)	
First generation Turkey or Morocco	215 (3.4)	1.1 (0.7-1.9)	
Second generation Turkey or Morocco	129 (2.0)	0.8 (0.4-1.9)	
First generation Surinam, Aruba or Netherlands-Antilles	219 (3.4)	0.8 (0.5-1.2)	
Second generation Surinam, Aruba or Netherlands-Antilles			
First generation other non-Western	138 (2.2)	0.2 (0.1-0.9)	
Second generation other non-Western			
	230 (3.6)	1.4 (0.9-2.1)	
	137 (2.2)	0.8 (0.4-1.7)	
Net monthly income per household			
High (≥ € 3051,-)	1087 (17.0)	Ref	
Middle (€ 1151,- - € 3050,-)	2950 (46.2)	1.5 (1.2-2.1)	
Low (≤ 1150,-)	1004 (15.7)	2.0 (1.5-2.8)	
Did not want to answer	1110 (17.4)	1.9 (1.4-2.6)	
Unknown	232 (3.6)	1.8 (1.1-3.0)	

3.1.6   *Conclusions and suggestions for the request for advice from the Health Council*
Protection against diphtheria induced by vaccination is long-lasting, even though the precise determinants for protection are not known. However, the antibody levels against diphtheria do decline during adulthood and although this is not reflected by a rise in cases, there is no such feeling that the current immunisation schedule includes too many immunisations. The current booster at four years of age, however, may be postponed or even skipped. In order to ensure lifelong protection against diphtheria a booster immunisation around the age of 18 may be considered.

3.1.7 *References*

1. Diphtheria, tetanus, and pertussis: recommendations for vaccine use and other preventive measures. Recommendations of the Immunization Practices Advisory committee (ACIP). MMWR Recomm Rep. 1991;40(RR-10):1-28.
2. Swart EM, van Gageldonk PG, de Melker HE, van der Klis FR, Berbers GA, Mollema L. Long-Term Protection against Diphtheria in the Netherlands after 50 Years of Vaccination: Results from a Seroepidemiological Study. PLoS One. 2016;11(2):e0148605.
3. Berbers G, van Gageldonk P, Kassteele JV, Wiedermann U, Desombere I, Dalby T, et al. Circulation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. Nat Commun. 2021;12(1):2871.
4. Ruijs WL, Hautvast JL, van der Velden K, de Vos S, Knippenberg H, Hulscher ME. Religious subgroups influencing vaccination coverage in the Dutch Bible belt: an ecological study. BMC Public Health. 2011;11:102.
5. Spaan DH, Ruijs WL, Hautvast JL, Tostmann A. Increase in vaccination coverage between subsequent generations of orthodox Protestants in The Netherlands. Eur J Public Health. 2017.
6. Ruijs WL, Hautvast JL, van Ijzendoorn G, van Ansem WJ, van der Velden K, Hulscher ME. How orthodox protestant parents decide on the vaccination of their children: a qualitative study. BMC Public Health. 2012;12:408.
7. van Lier A, van de Kassteele J, de Hoogh P, Drijfhout I, de Melker H. Vaccine uptake determinants in The Netherlands. Eur J Public Health. 2013.
8. Plotkin S, Orenstein WA, Offit PA. Vaccines. 7 ed2018.
9. Markina SS, Maksimova NM, Vitek CR, Bogatyreva EY, Monisov AA. Diphtheria in the Russian Federation in the 1990s. J Infect Dis. 2000;181 Suppl 1:S27-34.
10. Barrett DJ. Human immune responses to polysaccharide antigens: an analysis of bacterial polysaccharide vaccines in infants. Adv Pediatr. 1985;32:139-58.
11. Tetanus vaccines: WHO position paper - February 2017. Wkly Epidemiol Rec. 2017;92(6):53-76.
12. de Voer RM, Mollema L, Schepp RM, de Greeff SC, van Gageldonk PG, de Melker HE, et al. Immunity against Neisseria meningitidis serogroup C in the Dutch population before and after introduction of the meningococcal c conjugate vaccine. PLoS One. 2010;5(8):e12144.
13. Steens A, Mollema L, Berbers GA, van Gageldonk PG, van der Klis FR, de Melker HE. High tetanus antitoxin antibody concentrations in the Netherlands: a seroepidemiological study. Vaccine. 2010;28(49):7803-9.
14. Schurink-van 't Klooster TM. the National Immunisation Programme in the Netherlands; surveillance and developments in 2015-2016. Bilthoven: National Institute for Public Health and the Environment; 2016. Report No.: 2016-0141.
15. Jané M, Vidal MJ, Camps N, Campins M, Martínez A, Balcells J, et al. A case of respiratory toxigenic diphtheria: contact tracing results and considerations following a 30-year disease-free interval, Catalonia, Spain, 2015. Eurosurveillance. 2018;23(13):17-00183.

16. Brandon D, Kimmel M, Kuriyakose SO, Kostanyan L, Mesaros N. Antibody persistence and safety and immunogenicity of a second booster dose nine years after a first booster vaccination with a reduced antigen diphtheria-tetanus-acellular pertussis vaccine (Tdap) in adults. Vaccine. 2018;36(42):6325-33.
17. Halperin SA, Donovan C, Marshall GS, Pool V, Decker MD, Johnson DR, et al. Randomized Controlled Trial of the Safety and Immunogenicity of Revaccination With Tetanus-Diphtheria-Acellular Pertussis Vaccine (Tdap) in Adults 10 Years After a Previous Dose. J Pediatric Infect Dis Soc. 2019;8(2):105-14.

3.2 Pertussis

3.2.1 History of vaccination against pertussis

Whole cell pertussis (wP) vaccinations have been used in large-scale programmes in The Netherlands since 1952, with all cohorts born since 1945 invited. Vaccination against pertussis is part of the NIP from 1957 onwards. Late 2001, an acellular pertussis (aP) component was added to the preschool dT-IPV booster. From 2005 onwards, infant wP is replaced by aP components. In the current Dutch NIP, infants and children receive four or five aP containing vaccinations, depending whether the mother received a maternal Tdap vaccination during pregnancy. In this NIP schedule, with vaccine doses at (2)-3-5-11 months of age, aP is part of a hexavalent DTaP-IPV-Hib-HepB vaccine for infants (3 or 4 doses) and a dTap-IPV booster dose for 4-year-olds. From late 2019 onwards, aP is also administered through a Tdap vaccination advised to all pregnant women of 22w of gestation or more. To date, aP vaccines with 3 or 5 components are used within the NIP.

3.2.2 Goal of vaccination against pertussis

To prevent whooping cough in newborns, infants and young children (up to and including five years of age) because for them pertussis can result in severe disease requiring hospitalization or even death (1, 2).

3.2.3 Epidemiology of pertussis in The Netherlands

After the start of the NIP in 1957, in which a whole cell pertussis (wcP) combination vaccine was used, IR of pertussis decreased and remained low for about 30 years. In 1987, 2709 pertussis cases were notified.

In 1996, pertussis became endemic again in The Netherlands, with additional peaks in disease every 3-5 years (figure 1). From that moment onwards, pertussis became the most reported vaccine preventable disease in The Netherlands. Several changes regarding the pertussis vaccination schedule were implemented in the NIP. These changes did not impact the overall disease burden (see figure 1), but they did have an effect on the IR of pertussis in 6 months to 9 year olds (figure 2). However, IR in 0-5-month-olds remained high, indicating insufficient protection from the NIP. For better protection of this group, the pertussis vaccination during pregnancy was introduced late 2019. IR in people ≥10 years did not change either. The low IR in 2020 and 2021 are probable due to the measures to control the COVID-19 pandemic.
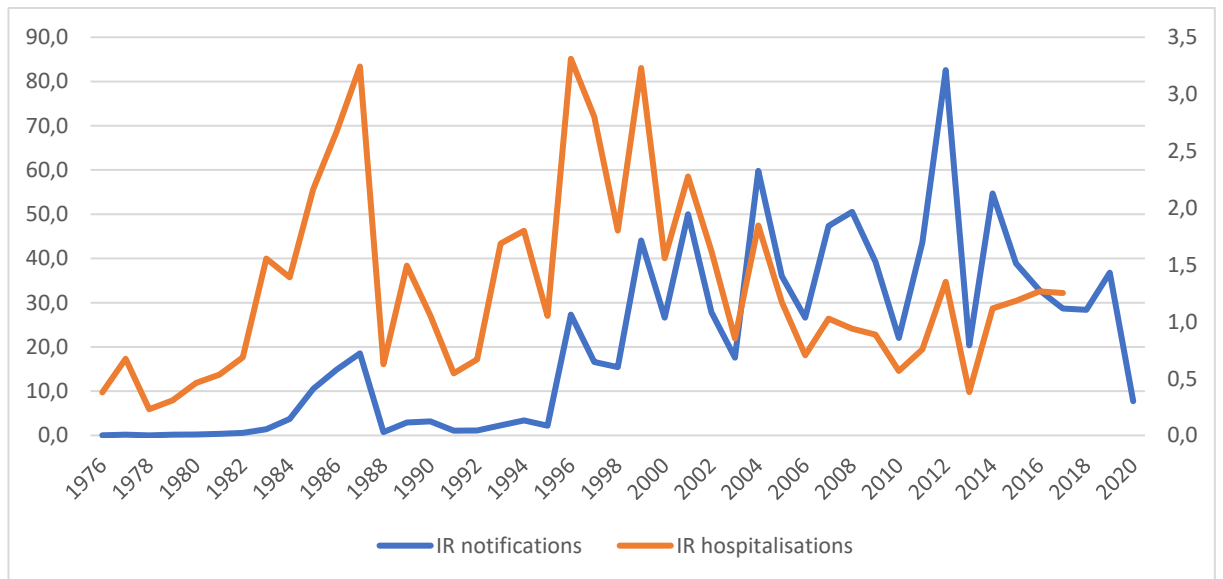
Figure 1 Pertussis notifications (left Y-axis) and hospitalizations (right Y-axis) per 100,000 for 2000-2021. Data on hospitalization are not available from 2019 onwards.
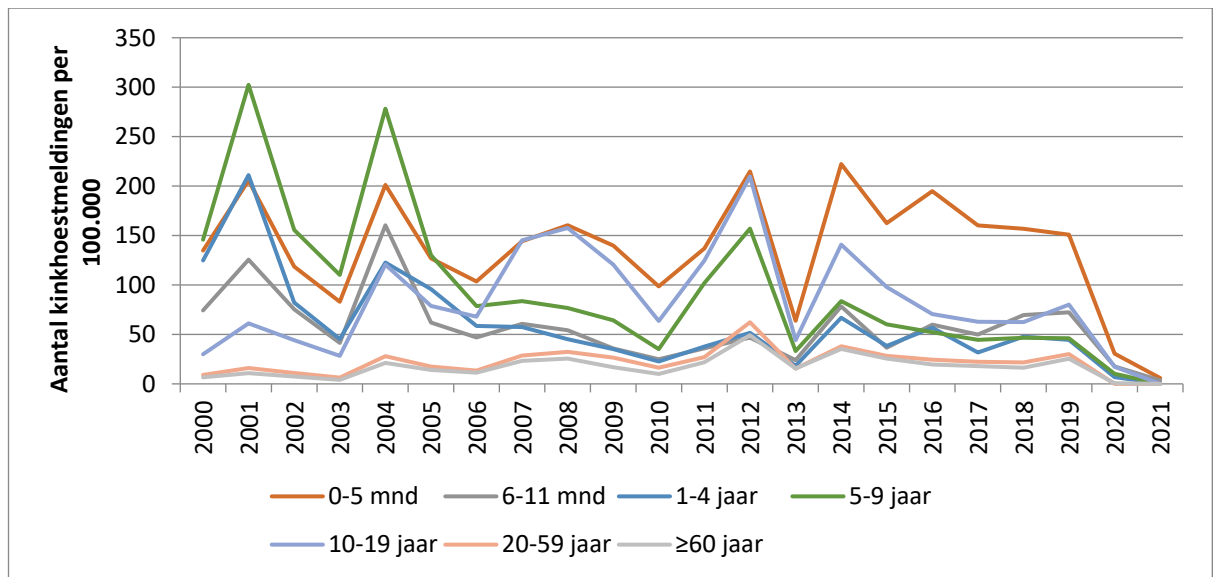
Figure 2 Pertussis notification per 100,000 per age category for 2005-2021*
Source: OSIRIS
*For 2021 notifications up to and including April 30 are depicted.

3.2.4   *Assessment of the vaccination against the six criteria, issues identified*
Criterion 1. Is the protection adequate for all those intended to be protected?
Up to 2019, pertussis notifications showed a relatively high incidence of disease in young, not yet (fully) vaccinated infants. Incidence rate (IR) of pertussis notifications is under control among 6-month-olds to 7-year-olds, probably due to the NIP. At older ages, IR increases again due to infection. Based on an advice of the Health Council, late 2019 dTap vaccination during pregnancy was introduced.

Issues related to criterion 1
- Can it be shown in the Dutch situation that the new NIP element of maternal pertussis vaccination is safe and effective for the protection of newborn and infants?

Criterion 2. Is the applied vaccination strategy optimal?
In relation to the goal of pertussis vaccination within the NIP, disease burden among infants and children up to and including five years of age is probably under control after implementation of the maternal pertussis vaccination. However, pertussis seroprevalence in people of 7 years and older is increasing, indicating recent infection. Currently, this age group is not the target of the NIP pertussis vaccination programme, but these people could transmit the infection to young, vulnerable infants.

Issues related to criterion 2
- What is the public health importance of increased incidence of pertussis among older children and adults?

Criterion 3. Does the programme include too much?
Current surveillance data do not suggest that the number of pertussis doses within the NIP is higher than needed. Infants of mothers who were vaccinated during pregnancy, receive one dose less than infant of unvaccinated mothers. However, some groups have been identified that receive an additional primary series dose at age 2 months even if their mother has been vaccinated with a pertussis vaccine during pregnancy more than two weeks before delivery. These groups are preterm born children, children of hepatitis positive mothers and children of immune compromised mothers, e.g. due to immune suppressive medication.

Issues related to criterion 3
- Is the additional vaccination at age 2 months still required for all identified specific groups (no or late maternal vaccination, preterm born infants, infants of hepatitis B positive mothers and infants of immune compromised mothers)?

Criterion 4. Does the programme include too little?
In the advice 'Vaccination against pertussis: goal and strategy ', the Health Council stated that the main goal of pertussis vaccination within the NIP is to prevent whooping cough in newborns, infants and young children up to and including five years of age. With the implementation of the maternal pertussis vaccination programme this goal is within reach. Vaccination coverages of the maternal and infant vaccinations programmes amount to ≈70% and ≈95%, respectively. Accurate estimates of the disease burden in adolescents, adults and the elderly are lacking. The changed vaccination policy – in which aP is used instead of wP – increases the risk of transmission in these age groups. Therefore, a relevant question is what the public health importance is of increased incidence of pertussis among older children and adults. Should the public vaccination programme target these groups too?

Issues related to criterion 4
- What is the public health importance of increased incidence of pertussis among older children and adults?

Criterion 5. Is the timing of immunisations using combination vaccines optimal or at least acceptable?

Several studies of humoral and cellular immunity following wP and aP vaccinations using a 2-3-4-months primary series and booster doses at 11 months and 4 years of age, show that the immune response is negatively impacted due to the relatively short intervals between primary series and booster doses. In The Netherlands, from 2020 onwards, infants of mothers who received a pertussis vaccination during pregnancy and are not part of specific risk groups (eg. preterms), are eligible for a 3-5-11-months vaccination schedule.

Issues related to criterion 5
- Prolonging the intervals between 1) the primary series and the booster dose at 11 months and 2) the booster doses at 11 months and 4 years of age should be discussed.

Criterion 6. Are there important drawbacks of the NIP? For the population as a whole? For those who opt out? How are these drawbacks to be weighed against the advantage of the programme and its components?

The resurgence of pertussis in the late nineties among older children and adults may be the combined result of changed population dynamics of pertussis infection and the establishment of new equilibria after 1) long-term mass immunisation of children, 2) introduction of aP-vaccines that are less effective in preventing transmission from the 90s, and 3) emergence of more virulent Bordetella pertussis strains. Pathogen surveillance also shows that the percentage of vaccine antigen deficient strains is increasing in The Netherlands and worldwide. In 2019, 27% of studied isolates (19/71) was Prn deficient.

To date, aP vaccines with 3 or 5 components are used in the NIP. In the Health Council advisory report of 2014, the Council concluded that current knowledge on the correlates of protection was insufficient to base the choice of vaccine on the number of pertussis antigens. It was also concluded that the clinical relevance of antigen deficient strains was unclear. It was recommended to perform further immunological research and field studies to establish the correlates of protection

A limitation of the acellular vaccines (aP) in current use is that they do not prevent transmission. Baboon models also show that the protection of aP vaccines against disease is limited to about 3-5 years (3).

Issues related to criterion 6
- Do vaccines with 2-, 3- or 5- pertussis antigens (Hexyon, Infanrix-hexa and Vaxelis) differ in effectiveness?
- Current aP vaccines are suboptimal to prevent transmission. Is there a need for improved pertussis vaccines in the long term that do prevent transmission and reduce circulation?

3.2.5   *Exploration of the issues against available evidence*
Can be shown in the Dutch situation that the new NIP element of maternal pertussis vaccination is safe and effective for the protection of newborn and infants?
In The Netherlands, maternal pertussis vaccination was implemented on December 16, 2019 (4). The vaccination is offered from 22 weeks of

gestation onwards. Midwifes and gynaecologists inform expectant mothers and direct them to the youth health centres, where women can ask for additional information and receive the vaccination.
A recent systematic review on the safety and effectiveness of maternal pertussis vaccination showed that VE estimates against pertussis up to 3m of age range between 69% and 93%, 94% against hospitalization and 95% against death (5).

Regarding the safety profile similar reassuring data are shown in this and other reviews (5-7). No differences in reactogenicity are found in pregnant compared with non-pregnant women. There is no increased risk of adverse pregnancy outcomes, except for a small increased risk of chorio-amnionitis, found in a few studies. However, in these studies no increased risk for preterm delivery, that is frequently caused by chorioamnionitis, was found (5-7). Therefore, experts doubt there is a causal relation between chorio-amnionitis and maternal pertussis vaccination.

In The Netherlands, for the first few months of 2020 preliminary results of the vaccine effectiveness (VE) of maternal pertussis vaccination against pertussis disease in young infants was estimated at 74% (-32 to 96%) (8). However, numbers are small. From March 2020 onwards, pertussis disease data are probably impacted by control measures against the SarsCov2 pandemic, such as social distancing, making and a reliable estimate on VE is impossible (9).

The coverage of maternal pertussis vaccination is about 70% (10).
The Dutch Pharmacovigilance Centre Lareb received 205 reports of Adverse Events Following maternal Tdap vaccination between December 16, 2019 and December 31, 2020 on a total of >110,000 maternal Tdap vaccinations (11). No new safety signals were reported.

What is the public health importance of increased incidence of pertussis among older children and adults?
The pertussis epidemiology up to and including 2019 showed that the infant pertussis vaccination schedule leads to a situation in which pertussis disease is low for infants of 6 months of age to children of 8-9 years of age (8) (figure 2). Additional protection for infants younger than 6 months will probably be provided by the maternal pertussis immunisation programme which was implemented recently.

Pertussis infection rates, however, show increasing trends in older children, adolescents, adults and elderly. This is shown by data of the consecutive serosurveillance studies (Pienter1-3) (12) (Versteegen, P et al., manuscript accepted for publication). Increasing percentages of older children and adults with anti-PT antibodies ≥100 IU/mL, indicating a recent infection with pertussis are seen. In Pienter1 (1995-1996) (≥10 years olds) this percentage was 1.0%, in Pienter 2 (2006-2007) and Pienter 3 (2016-2017) (≥7 years olds) it amounted to 3.5% and 5.9%, respectively.
Zooming in on age stratified seroprevalence rates, some differences between Pienter 2 and Pienter 3 are seen (figure 3).
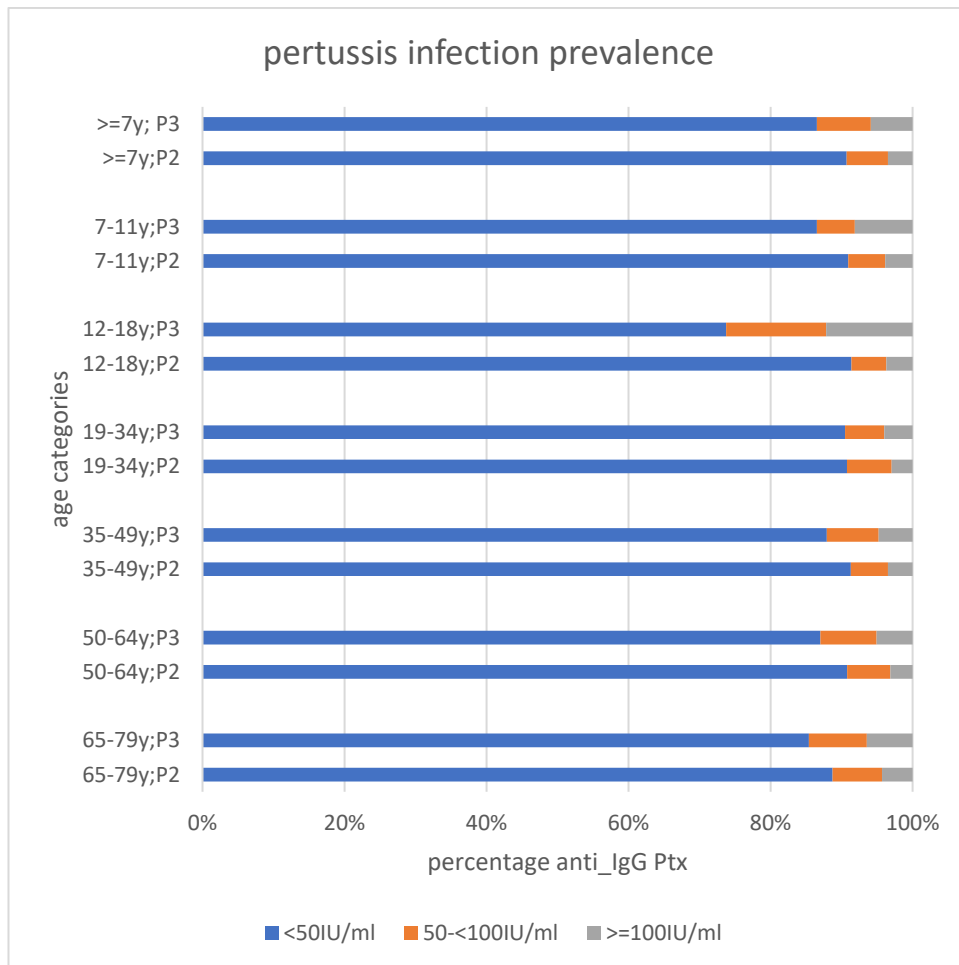
Figure 3 Anti IgG PT seroprevalence per age group for Pienter 2 (2006-2007) and Pienter 3 (2016-2017).

For all age groups of 7 years and older, the percentage of participants with an infection induced anti-PT antibody concentration of ≥100 IU/mL is higher in the P3 sample than in the P2 sample. For 7-11 and 12-18 year olds this difference is significant: 8.1% vs 3.9% in 7-11 year olds and 12.2% vs 3.7% in 12-18 year olds.

Differences in priming between the 7-11 year olds may play a role. The P2 participants were whole cell primed whereas the P3 participants were primed with an acellular pertussis vaccine. Figure 2 suggests that the P3 group was not well protected by the 4y booster during 2012 and 2014, two years with increased pertussis occurrence.

This latter aspect also may have played a role in the 12-18-year-olds. Furthermore, in this 12-18 year old group the P3 group was eligible for the 4y booster and the P2 group was not.
The increasing pertussis infection rates among older children, adolescents and adults increase the risk of transmission in the community and may put the affected age groups at health risks due to pertussis. A recent systemic review on the pertussis burden in older adults indicated a considerable underestimation of the pertussis burden by comparing notification rates with seroprevalence data (13). Only few

studies assessing the costs associated with pertussis morbidity and mortality could be included and no firm conclusion could be drawn on this aspect.

aP primed girls (birth cohort 2005 and later) will reach childbearing age in 5 to 10 years. It is not known yet whether this aP priming will influence the effectiveness of the maternal pertussis vaccination, especially if this goes along with increasing rates of pertussis antigen deficient strains.
For an extensive discussion whether or not the NIP should target older children and adults for prevention of pertussis, more data should be collected.

Is the additional vaccination at age 2 months still required for all identified specific groups (i.e. no or late maternal vaccination, preterm born infants and infants of hepatitis B positive mothers)?
Simultaneously with the implementation of the maternal pertussis vaccination, a change in the infant NIP was implemented. Term infants of mothers, who received Tdap during pregnancy, receive a reduced and postponed infant pertussis vaccination schedule with DTaP-IPV-Hib-HepB vaccinations at 3, 5 and 11 months of age (14). Some infants continue to receive an fourth vaccination earlier in life, i.e. a 2-3-5-11 months schedule. These groups are:
- infants of mothers who were not vaccinated during pregnancy;
- preterm infants;
- infants born within 2 weeks after maternal vaccination;
- infants of mothers with a possibly reduced transplacental transfer of antibodies, e.g. mothers receiving immune suppressive medication.

The reduced and postponed schedule was based on the MIKI-study, in which infants of mothers who received a Tdap vaccine at 30-32w GA and infants of during pregnancy unvaccinated mothers both received a 3-5-11-months vaccination schedule (15).

Currently the PIMPI-study (Preterm Infants and Maternal Pertussis Immunisation) is ongoing at RIVM. In this study, expectant mothers with a maternal pertussis vaccination between 20 and 24 week of gestation are asked to participate in a study to assess pertussis-specific antibody concentrations in term and preterm infants at birth and at 2 months of age. Results are expected in 2022. The goal of this study is to:
1. confirm results of the postponed and reduced NIP vaccination schedule of the MIKI-study in the light of a maternal pertussis vaccination earlier throughout gestation.
2. Explore whether (a subset of) preterm infants also can receive a reduced and postponed vaccination schedule if the mother is vaccinated in the proper time window.

[The following paragraph is relevant for the hepatitis B chapter that will follow later. Here we include it for information.
For infants of hepatitis B carrier mothers, the additional DTaP-IPV-Hib-HepB vaccination at 2 months is given to prevent the contraction of

hepatitis B. This risk is high for these infants. In Norway, all infants receive a 3-5-12m vaccination schedule without a maternal pertussis vaccination programme in place. In addition to this programme, infants of hepatitis B carrier mothers receive hepatitis B immune globulins and a first hepatitis B vaccination at birth, followed by another hepatitis B dose at 1 month of age. Therefore, the schedule for infants of hepatitis B carrier mothers in Norway (0-1-3-5-12 months) resembles the schedule in The Netherlands (0-2-3-5-11 months), As far as we know, information whether a vaccination schedule with a 3 months interval between the birth dose of hepatitis B and the doses of the primary series (i.e. a 0-3-5-11 months hepatitis vaccination schedule) in infants of hepatitis carrier mothers still can prevent vertical hepatitis transmission, is not available. Because timely protection against hepatitis B is very important for these infants, the currently used schedule for this group should not be changed.]

The impact of immune suppressive treatment on the immune response of the maternal pertussis vaccination and the transplacental antibody transfer will be explored in approximately 60 women with rheumatoid arthritis, who receive different regimens of disease modifying medication. Pertussis specific antibodies will be determined in blood samples at 20 and 30 weeks of gestation (i.e. before and after vaccination) and in cord blood. Results will be compared with data derived from healthy pregnant women and their offspring (MIKI-data) and are expected in mid-2022. Further and more robust data on the influence of immune suppressive medication are needed before a change in vaccination policy regarding infants of this specific, growing group of pregnant women is possible, because immune response and transplacental antibody transfer show great variation (15).

The current pertussis epidemiology (2020-2021) is strongly influenced by the measures to prevent the COVID-19 pandemic. This not only prohibits a good evaluation of the maternal pertussis vaccination but also leads to incomplete data on the pertussis epidemiology in general. Therefore, no conclusions can be drawn now that support a change of the pertussis vaccination schedule in infants of unvaccinated mothers. Similarly, for all groups that receive a 2-3-5-11 months vaccination schedule and are born of a vaccinated mother no additional information is available to evaluate and possibly change the schedule. For preterm infants and infants of mothers who use immunosuppressive medication, new data will be available in 2022. These data may lead to a change of the currently advised schedule.

Prolonging the intervals between 1) the primary series and the booster dose now at 11 months and 2) the booster doses now at 11 months and 4 years of age, should be considered
Infants in The Netherlands receive several high doses of aP vaccine in their first year of life: the doses of the primary series at 3 and 5 month of age (plus 2 months of age if the mother was not vaccinated during pregnancy) and the first booster dose at 11 months of age. WHO recommends the first booster dose to be given between 11 and 24 months with an interval of at least 6 months from the last dose of the primary series. No data are available comparing vaccine efficacy or induced immune responses of vaccinations schedules with varying

intervals between the last dose of the primary series and the first booster dose.

This immunisation schedule results in high antibody levels at preschool age, but also in high T-cell cytokine levels potentially associated with adverse events and the presence of more terminally differentiated CD4+ T-cells. Fewer doses and longer intervals between aP vaccinations would seem appropriate (16-21). T-cell cytokine levels were still high in aP-primed children at 4 years of age, 3 years after the infant vaccinations, and did not further increase upon the pre-school booster vaccination which suggests that pertussis-specific T-cell memory is still present (4-5). Moreover, infants are already partially protected against severe pertussis after the first one or two vaccinations (88). Furthermore, several studies showed a low PT-IgG seroprevalence and pertussis incidence in aP-primed children up to 6 years of age (22) (23-25), which implies that the pre-school booster vaccination currently administered at 4 years of age could be postponed with 1 or 2 years. This may also result in lower numbers of local adverse events reported after the current fifth aP vaccination at preschool age. Severity and number of local adverse events decreases with increasing age. An aP immunisation schedule of vaccinations administered at 3, 5 and 12–15 or even 18 months of age combined with a low dose aP booster vaccination at 5–6 years of age would be preferable. Potential effects on vaccination coverage and (long-term) immunological effects of such a change should be monitored, as well as the presumed favourable effect on adverse events. In relation to AEFI, not only the timing but also the antigen content influences reactogenicity (Signals_2020_Extensive swelling of the vaccinated limb_switch_InfanrixIPV_Boostrix_UPDATE.pdf (lareb.nl) (26). Disentangling both aspects will be challenging.

Do vaccines with 2-, 3- or 5- pertussis antigens (Hexyon, Infanrix-hexa and Vaxelis) differ in effectiveness?
The first pertussis vaccines were whole cell vaccines (wP), consisting of heat-inactivated bacteria. Nowadays in The Netherlands and many other high-income countries only acellular pertussis (aP) vaccines, developed for their superior safety record, are being used.

aP vaccines can contain 1 to 5 purified immunogenic proteins from the bacterium. From the introduction of infant aP vaccines in The Netherlands (January 2005), vaccines with three (Pertussis Toxoid (PT), filamentous heamagglutinin (FHA) and pertactin (Prn)) or five pertussis antigens (PT, FHA, Prn and Fimbriae 2 and 3 (Fim2/3)) were used.
A number of efficacy trials of the second generation of aP vaccines, performed in the 1980's and 1990's, have incorporated the first generation of wP vaccines as comparators. They showed that both wP vaccines as well as aP vaccines vary substantially in efficacy. For wP vaccines efficacy estimates ranged between 36% and 98% (27). In their 2004-advice on pertussis vaccination, the Health Council stated that the effectiveness of the Dutch whole cell pertussis vaccine against pertussis disease was high up to and including 1993, but strongly declined thereafter (28). A blinded RCT, performed in Senegal, showed that wP was 55% efficacious against less severe pertussis versus 96% for severe pertussis (29). No differences in efficacy between 3 vs 5-component aP vaccines were observed, but aP vaccines with 1 or 2 components showed lower efficacy estimates than aP vaccines with ≥3 components

(1). However, in more long term observational studies, no difference in vaccine effectiveness was found in relation to the number of aP components.

For the NIP of The Netherlands, each year the vaccine effectiveness (VE) of the infant vaccination series is estimated using the screening method (30). From 2005 onwards, VE in 1-3-year-olds against pertussis disease ranged between 43% (3-year-olds, whole cell primed, 2006) and 98% (1-year-olds, aP primed, 2016 and 2018) (figure 5). Currently available surveillance data in The Netherlands are not equipped to estimate product specific VE, distinguishing possible difference in VE between 3- and 5 component pertussis aP vaccines.
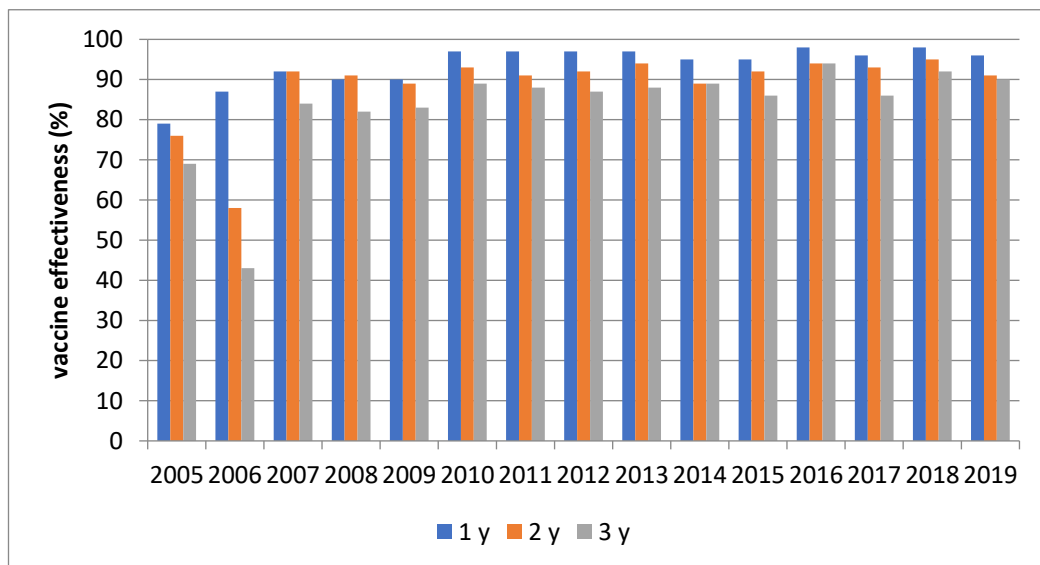

Figure 4 Vaccine effectiveness against pertussis disease in 1, 2 and 3 year olds using the screening method for 2005-2019.

At present infant aP vaccines authorized for the Dutch market contain besides components protecting against tetanus, diphtheria, Hib, hepatitis B, and polio two, three or five components for protection against pertussis: PT and FHA (Hexacima, Hexyon), PT, FHA and Prn (Infanrix-hexa) and PT, FHA, Prn, Fim2/3 (Vaxelis). The number and combination of aP vaccine components determine the breadth and basis for protective B-and T cell responses. Antibodies to PT are thought to protect from disease by neutralizing this disease-associated toxin when released, while antibodies to the adhesins FHA, Prn and Fim2/3 embedded in the bacterial cell surface could prevent infection through different mechanisms, e.g. bactericidal activity (31, 32). In a recent report Prn was found to be the only one of the 5 aP components responsible for generating bactericidal antibodies to *B. pertussis* (33). The study suggested that the emergence and the widespread circulation of Prn-deficient strains is driven by aP vaccination and the generation of bactericidal antibodies targeting Prn. In Dutch *B. pertussis* isolates, after a decrease in Prn deficiency observed in from 2015 to 2017, a sharp increase is seen in 2018 and 2020 up to May 1st (8). In other countries, the prevalence of Prn-deficiency has even reached around 80% (34, 35). Ongoing emergence of vaccine-antigen-deficient (VAD) strains

impacting aP VE is of concern. Also, these observations underscore different protective mechanisms of the 5 virulence factors and vaccine antigens PT and Prn versus FHA and Fim2/3 in aP vaccines.

In conclusion, due to a lack of well-established correlates of protection, no firm conclusions can be drawn about vaccine effectiveness of pertussis vaccines relative to the number of antigens.

Current aP vaccines are suboptimal to prevent transmission. Is there a need for improved pertussis vaccines in the long term that do prevent transmission and reduce circulation?
Acellular pertussis vaccines have been suggested to protect from disease but failing to prevent colonization. Evidence for this comes from controlled preclinical experimental challenge models. Baboon models indicated that aP vaccines are less efficacious against transmission than wP vaccines (1, 3) and mouse models revealed that aP vaccination is associated with prolonged carriage of *B. pertussis* by a suppression-mechanism of mucosal Th17 memory responses. Over the last decades, vaccine research in these preclinical models as well as in humans has elucidated the fundamental disparity between wP- an aP-primed immune responses. Whereas wP vaccines, similar to natural infections, predominantly induce so-called Th1 and Th17 type of immunity, aP vaccines promote a strong Th2 type component, reflected by the production of different sets of Th-derived indicator cytokines, IFNγ,/IL17 and IL4/IL-5/IL-13 respectively (17, 36-39). These cytokine classes are associated with profound different modes of protective capacity, the pro-inflammatory cytokines IFNγ and IL17 being superior in promoting opsonophagocytosis and clearance of *B. pertussis* by phagocytes (40). As suggested by the mouse model, aP vaccine-induced immunity could lead in humans to asymptomatic carriers spreading the disease to susceptible non- or partially-immunized individuals or individuals with waned immunity. Furthermore, aP-induced Th2-skewed immunity seems to be associated with a shorter duration of protection from disease, as indicated by various epidemiological studies (41, 42) .

The accumulating evidence is that aP vaccines induce a rather unfavourable Th2-dominated type of immunity associated with a shorter duration of protection and without interrupting transmission. This evidence has led to renewed interest in the development of a third generation of improved pertussis vaccines by pharma. For this, enhanced knowledge of immune correlates of protection and public-private efforts are required (43). Various vaccine concepts are underway with the profile to induce Th1/Th17 type immunity at the respiratory mucosae, to target a large set of vaccine antigens, and to be capable of interrupting transmission (44). The furthest in development is the live attenuated whole cell pertussis vaccine candidate BPZE1, being extensively tested in preclinical phase and safely administered to > 350 individuals in various phase 1 and phase 2 clinical trials to date (45). Even if the implementation of maternal vaccination is highly efficacious to prevent pertussis in newborns, high circulation of this human-only-adapted pathogen forms a risk for high yearly disease incidence as well as epidemic outbreaks among other age-groups, including frail elderly, due to waning (vaccine-induced) immunity. From a public health

perspective, new pertussis vaccines that prevent transmission and reduce circulation would be highly advantageous.

3.2.6   *Conclusions and suggestions for the request for advice from the Health Council*
The recently implemented maternal vaccination against pertussis provides valuable added protection of young infants. However, due to COVID-19 evidence for a favourable effect in The Netherlands is still limited to date. Introducing the pertussis vaccination of expecting mothers, made it possible to reduce the number of vaccine doses for infants of vaccinated mothers. The vaccine dose at two months of age for infants born preterm, infants born to mothers with no or late maternal vaccination or with a possibly reduced transplacental transfer of antibodies needs to be maintained based on the evidence available to date. New data on this topic are expected in 2022.
The current immunisation schedule, using acellular pertussis vaccines, with a first booster at 11 month age and a second booster at 4 years of age results in high antibody levels at preschool age, but also in high T-cell cytokine levels potentially associated with adverse events and the presence of more terminally differentiated CD4+ T-cells. The occurrence of adverse events following repeated aP containing booster doses is probably also impacted by antigen dose and timing of the vaccination. Fewer doses and longer intervals between aP vaccinations seem appropriate. With the aP vaccines currently available such a schedule could comprise primary vaccinations at 3 and 5 months of age and a first booster at 12–15 or even 18 months and a low dose booster at the age of 5–6 years. From a public health perspective, however, there is need for a new type of pertussis vaccines that do not induce a Th2-dominated type of immunity and that do prevent transmission and reduce circulation.

3.2.7   *References*
1. Plotkin S, Orenstein WA, Offit PA. Vaccines. 7 ed2018.
2. Gezondheidsraad. Vaccinatie tegen kinkhoest: doel en strategie. Den Haag: Gezondheidsraad; 2015.
3. Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(2):787-92.
4. Schurink-van 't Klooster TM, De Melker H. the National Immunisation Programme of the Netherlands; surveillance and developments in 2018-2019. Bilthoven: the National Institute for Public Health and the Environment; 2019.
5. Campbell H, Gupta S, Dolan GP, Kapadia SJ, Kumar Singh A, Andrews N, et al. Review of vaccination in pregnancy to prevent pertussis in early infancy. J Med Microbiol. 2018;67(10):1426-56.
6. Vygen-Bonnet S, Hellenbrand W, Garbe E, von Kries R, Bogdan C, Heininger U, et al. Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. BMC Infect Dis. 2020;20(1):136.
7. D'Heilly C, Switzer C, Macina D. Safety of Maternal Immunization Against Pertussis: A Systematic Review. Infect Dis Ther. 2019.

8. Pluijmaekers AJM, de Melker HE. The National immunisation programme in the Netherlands; surveillance and developments in 2020-2021. Bilthoven: the National Institute for Public Health and the Environment; 2021.
9. Middeldorp M, van Lier A, van der Maas N, Veldhuijzen I, Freudenburg W, van Sorge NM, et al. Short term impact of the COVID-19 pandemic on incidence of vaccine preventable diseases and participation in routine infant vaccinations in the Netherlands in the period March-September 2020. Vaccine. 2021.
10. van Lier A, Oomen P, Giesbers H, van Vliet H, Hament J-M, Drijfhout I, et al. Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2020. Bilthoven: RIVM; 2021.
11. Lareb pC. Meldingen van bijwerkingen na maternale kinkhoestvaccinatie. 's Hertogenbosch: pharmacovigilance Centre Lareb, 2021.
12. de Greeff SC, de Melker HE, van Gageldonk PG, Schellekens JF, van der Klis FR, Mollema L, et al. Seroprevalence of Pertussis in the Netherlands: Evidence for Increased Circulation of Bordetella pertussis. PloS one. 2010;5(12):e14183.
13. Kandeil W, Atanasov P, Avramioti D, Fu J, Demarteau N, Li X. The burden of pertussis in older adults: what is the role of vaccination? A systematic literature review. Expert Rev Vaccines. 2019;18(5):439-55.
14. Gezondheidsraad. Vaccinatieschema zuigelingen na maternale kinkhoestvaccinatie. Den Haag: Gezondheidsraad; 2018. Report No.: 2018/27.
15. Barug D, Pronk I, van Houten MA, Versteegh FGA, Knol MJ, van de Kassteele J, et al. Maternal pertussis vaccination and its effects on the immune response of infants aged up to 12 months in the Netherlands: an open-label, parallel, randomised controlled trial. Lancet Infect Dis. 2019;19(4):392-401.
16. van der Lee S, Hendrikx LH, Sanders EAM, Berbers GAM, Buisman AM. Whole-Cell or Acellular Pertussis Primary Immunizations in Infancy Determines Adolescent Cellular Immune Profiles. Front Immunol. 2018;9:51.
17. van der Lee S, Sanders EAM, Berbers GAM, Buisman AM. Whole-cell or acellular pertussis vaccination in infancy determines IgG subclass profiles to DTaP booster vaccination. Vaccine. 2018;36(2):220-6.
18. van der Lee S, Kemmeren JM, de Rond LGH, Ozturk K, Westerhof A, de Melker HE, et al. Elevated Immune Response Among Children 4 Years of Age With Pronounced Local Adverse Events After the Fifth Diphtheria, Tetanus, Acellular Pertussis Vaccination. Pediatr Infect Dis J. 2017;36(9):e223-e9.
19. de Rond L, Schure RM, Ozturk K, Berbers G, Sanders E, van Twillert I, et al. Identification of pertussis-specific effector memory T cells in preschool children. Clin Vaccine Immunol. 2015;22(5):561-9.
20. Schure RM, Hendrikx LH, de Rond LG, Oztürk K, Sanders EA, Berbers GA, et al. T-cell responses before and after the fifth consecutive acellular pertussis vaccination in 4-year-old Dutch children. Clin Vaccine Immunol. 2012;19(11):1879-86.
21. Hendrikx LH, de Rond LG, Ozturk K, Veenhoven RH, Sanders EA, Berbers GA, et al. Impact of infant and preschool pertussis vaccinations on memory B-cell responses in children at 4 years of age. Vaccine. 2011;29(34):5725-30.

22. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med. 2012;367(11):1012-9.

23. Hallander HO, Andersson M, Gustafsson L, Ljungman M, Netterlid E. Seroprevalence of pertussis antitoxin (anti-PT) in Sweden before and 10 years after the introduction of a universal childhood pertussis vaccination program. APMIS. 2009;117(12):912-22.

24. Hallander HO, Gustafsson L, Ljungman M, Storsaeter J. Pertussis antitoxin decay after vaccination with DTPa. Response to a first booster dose 3 1/2-6 1/2 years after the third vaccine dose. Vaccine. 2005;23(46-47):5359-64.

25. Guiso N, Njamkepo E, Vie le Sage F, Zepp F, Meyer CU, Abitbol V, et al. Long-term humoral and cell-mediated immunity after acellular pertussis vaccination compares favourably with whole-cell vaccines 6 years after booster vaccination in the second year of life. Vaccine. 2007;25(8):1390-7.

26. Rennels MB. Extensive swelling reactions occurring after booster doses of diphtheria-tetanus-acellular pertussis vaccines. Semin Pediatr Infect Dis. 2003;14(3):196-8.

27. Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. N Engl J Med. 1996;334(6):349-55.

28. Gezondheidsraad. Vaccinatie tegen kinkhoest. Den Haag: Gezondheidsraad; 2004. Report No.: 2004/04.

29. Simondon F, Preziosi MP, Yam A, Kane CT, Chabirand L, Iteman I, et al. A randomized double-blind trial comparing a two-component acellular to a whole-cell pertussis vaccine in Senegal. Vaccine. 1997;15(15):1606-12.

30. Farrington CP. Estimation of vaccine effectiveness using the screening method. Int J Epidemiol. 1993;22(4):742-6.

31. Fothergill LD, Wright J. Influenzal meningitis the relation of age incidence to the bactericidal power of blood against the causal organism. J Immunol. 1933;24:273-84.

32. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med. 1969;129(6):1307-26.

33. Lesne E, Cavell BE, Freire-Martin I, Persaud R, Alexander F, Taylor S, et al. Acellular Pertussis Vaccines Induce Anti-pertactin Bactericidal Antibodies Which Drives the Emergence of Pertactin-Negative Strains. Front Microbiol. 2020;11:2108.

34. Lam C, Octavia S, Ricafort L, Sintchenko V, Gilbert GL, Wood N, et al. Rapid increase in pertactin-deficient Bordetella pertussis isolates, Australia. Emerg Infect Dis. 2014;20(4):626-33.

35. Martin SW, Pawloski L, Williams M, Weening K, DeBolt C, Qin X, et al. Pertactin-negative Bordetella pertussis strains: evidence for a possible selective advantage. Clin Infect Dis. 2015;60(2):223-7.

36. Ross PJ, Sutton CE, Higgins S, Allen AC, Walsh K, Misiak A, et al. Relative contribution of Th1 and Th17 cells in adaptive immunity to Bordetella pertussis: towards the rational design of an improved acellular pertussis vaccine. PLoS Pathog. 2013;9(4):e1003264.

37. van der Lee S, van Rooijen DM, de Zeeuw-Brouwer ML, Bogaard MJM, van Gageldonk PGM, Marinovic AB, et al. Robust Humoral and Cellular Immune Responses to Pertussis in Adults After a First Acellular Booster Vaccination. Front Immunol. 2018;9:681.
38. Schure RM, Hendrikx LH, de Rond LG, Ozturk K, Sanders EA, Berbers GA, et al. Differential T- and B-cell responses to pertussis in acellular vaccine-primed versus whole-cell vaccine-primed children 2 years after preschool acellular booster vaccination. Clin Vaccine Immunol. 2013;20(9):1388-95.
39. Hendrikx LH, Schure RM, Ozturk K, de Rond LG, de Greeff SC, Sanders EA, et al. Different IgG-subclass distributions after whole-cell and acellular pertussis infant primary vaccinations in healthy and pertussis infected children. Vaccine. 2011;29(40):6874-80.
40. Lambert EE, Buisman AM, van Els C. Superior B. pertussis Specific CD4+ T-Cell Immunity Imprinted by Natural Infection. Adv Exp Med Biol. 2019;1183:81-98.
41. Witt MA, Arias L, Katz PH, Truong ET, Witt DJ. Reduced risk of pertussis among persons ever vaccinated with whole cell pertussis vaccine compared to recipients of acellular pertussis vaccines in a large US cohort. Clin Infect Dis. 2013;56(9):1248-54.
42. Klein NP, Bartlett J, Fireman B, Baxter R. Waning Tdap Effectiveness in Adolescents. Pediatrics. 2016;137(3):e20153326.
43. Diavatopoulos DA, Mills KHG, Kester KE, Kampmann B, Silerova M, Heininger U. PERISCOPE: road towards effective control of pertussis. Lancet Infect Dis. 2019;19.
44. Locht C. The Path to New Pediatric Vaccines against Pertussis. Vaccines (Basel). 2021;9(3).
45. Jahnmatz M, Richert L, Al-Tawil N, Storsaeter J, Colin C, Bauduin C, et al. Safety and immunogenicity of the live attenuated intranasal pertussis vaccine BPZE1: a phase 1b, double-blind, randomised, placebo-controlled dose-escalation study. Lancet Infect Dis. 2020;20(11):1290-301.

3.3 Tetanus

3.3.1 *History of vaccination against tetanus*

Tetanus toxoid (TT) vaccinations have been used in large-scale programmes in The Netherlands since 1952, with all cohorts born since 1945 invited. Vaccination against tetanus is part of the NIP from 1957 onwards. In the current Dutch NIP, infants and children receive five or six TT containing vaccinations, depending whether the mother received a maternal Tdap vaccination during pregnancy. In this NIP schedule, TT is part of a hexavalent DTaP-IPV-Hib-HepB vaccine for infants (3 or 4 doses), a dTap-IPV booster dose for 4-year-olds and a dT-IPV booster dose at 9 years of age. Furthermore, TT is the carrier protein of the currently used MenACWY vaccination at 14 months and 14 years of age and one Pneumococcal serotype in the 10-valent pneumococcal conjugate vaccine, given at 3, 5 and 11 months of age. From late 2019 onwards, tetanus is also administered through the Tdap vaccination, advised to all pregnant women of 22w of gestation or more.

3.3.2 *Goal of vaccination against tetanus*

The main goal of vaccination against tetanus is the prevention of all tetanus disease in all ages, because tetanus can lead to death or severe

disease requiring hospitalization. Tetanus cannot be transmitted between persons. Therefore, herd immunity doesn't play a role.

3.3.3 *Epidemiology of tetanus in The Netherlands*

In The Netherlands, the yearly number of tetanus cases remained ≤ 5 from 2009 onwards, with one death reported in 2011 (figure 1). Cases mainly occurred among older individuals who were born before introduction of mass vaccination campaigns against tetanus and received insufficient tetanus post-exposure prophylaxis or did not consult a physician with a contracted wound.
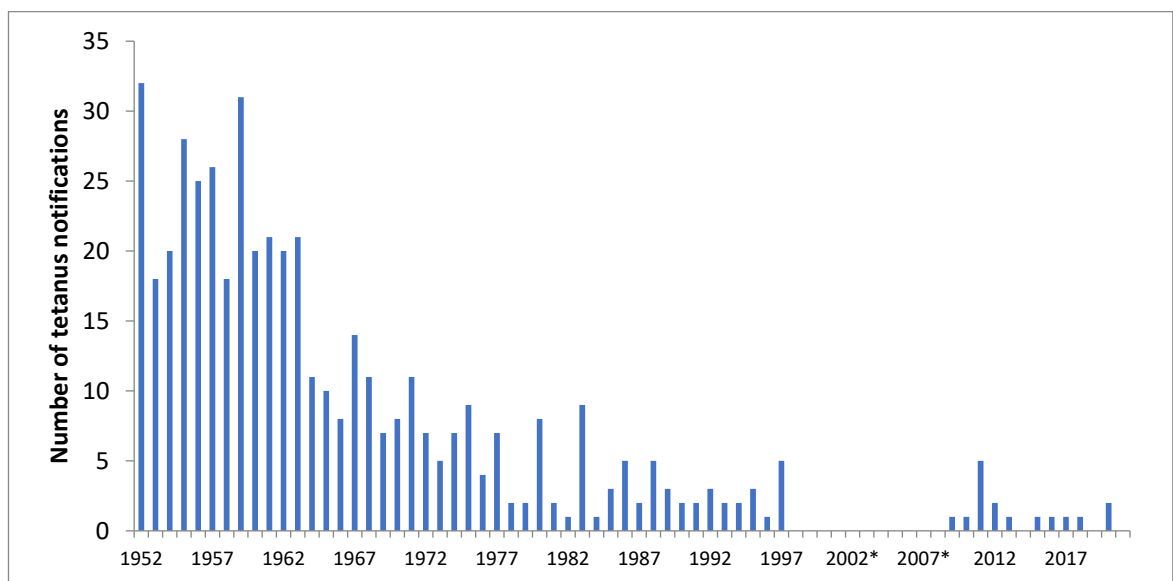
Figure 1 Reported cases of tetanus in The Netherlands by year, 1952-2021^.
*Between 1999 and 2009 tetanus was not notifiable.
^ For 2021, notifications up to and including May were included.

3.3.4 *Assessment of the vaccination against the six criteria, issues identified*

Criterion 1. Is the protection adequate for all those intended to be protected?

Immunosurveillance shows high anti-tetanus antibodies in the national sample with slow waning of humoral immunity. However, seroprevalence in orthodox protestants is much lower. This seroprevalence is assessed using two cut-off points i.e. 0.01 IU/mL (basic protection, not always sufficient in case of complex, deep and necrotic wounds) and 0.1 IU/mL (more robust, long term protection).

Issues related to criterion 1
- The protection of orthodox protestant people that reject vaccination, is low.
- It is uncertain which cut-off for protection should be used to assess the protection against tetanus in the population.
- The contribution of cellular immunity is unclear.

Criterion 2. Is the applied vaccination strategy optimal?
From the start of the NIP, vaccination coverage of vaccines targeting tetanus has been continually high in The Netherlands. The number of tetanus notifications ranges between 0 and 5 cases each year since 2009. From 2000 onwards, in total 5 people died due to tetanus (3 in 2001, 1 in 2003 and 2011). All five were 50 years or older and probably not vaccinated. These surveillance data suggest that the applied vaccination strategy against tetanus works well.

Criterion 3. Does the programme include too much?
The current NIP includes 7 or 8 TT containing vaccinations (including the boosting due to TT carrier proteins in the MenACWY vaccination for toddlers and teenagers), that are able to elicit a primary or booster immune response. Furthermore, the implemented Tdap vaccination during pregnancy is also a booster dose in previously vaccinated women, with 70% vaccination coverage. WHO advises 6 doses. Taking into account the very low disease burden and high seroprevalence, the current vaccination strategy protects very well.

International data and additional research suggest that the number of TT containing vaccinations can be lowered. TT is often given in combination with diphtheria toxoid. Spreading the TT booster doses could further prolong the high tetanus seroprevalence and probably also have a positive impact on the protection against diphtheria.

Besides TT vaccination within the NIP, TT is also regularly advised as tetanus post-exposure prophylaxis (T-PEP). Another aspect of T-PEP is the use of Tetanus Immune Globulins (TIG) to prevent tetanus on the short term. A Dutch study showed underuse of TIG, while in contrast, the study showed overuse of TT. Analyses of the second Pienter study also point in this direction. Therefore, adherence to the guideline can be improved regarding use of TIG. Furthermore, an update of the need of TT as post exposure prophylaxis measure and the interval of TT boosters during adulthood should discussed.

Issues related to criterion 3
- What is the impact of tetanus toxoid as a carrier protein in conjugated vaccines? Should elicited immune responses due to TT carrier proteins be counted as booster doses? What are possible consequences?
- The number of NIP booster doses could be lowered.
- The necessity of booster doses at adult age is uncertain.
- The Health Council T-PEP guideline needs updating and adherence should be improved.

Criterion 4. Does the programme include too little?
No, there is no evidence that the programme has insufficient impact.

Criterion 5. Is the timing of immunisations using combination vaccines optimal or at least acceptable?
For long-term and persisting tetanus protection in all age groups, WHO recommends at least three TT containing booster doses, preferably in the second year of life, between 4 and 7 years of age and between 9 and 15 years of age. The Dutch vaccination schedule is in line with these

recommendations. However, seroprevalence data suggest that the interval between the TT containing booster doses within the NIP can be extended. The same holds for the use of TT in relation to T-PEP.

Issues in relation to criterion 5
- Spreading the TT booster doses could further prolong the high tetanus seroprevalence
- The Health Council T-PEP guideline needs updating.

Criterion 6. Are there important drawbacks of the NIP? For the population as a whole? For those who opt out? How are these drawbacks to be weighed against the advantage of the programme and its components?
No important drawbacks in relation to the public vaccination programme against tetanus are known.

3.3.5   *Exploration of the issues against the available knowledge*
The protection of orthodox protestant people is low
Tetanus seroprevalence in orthodox protestants was 36% (95%CI 17-57%), as assessed in the Pienter 2 serosurveillance study (2). It is a well-known fact that The Netherlands includes groups of socio-geographically clustered people who refuse vaccination on religious grounds. These groups comprise approximately 220,000 members (i.e. 1.3% of the Dutch population; reference date 1-1-2006) (3). About three quarter live in a municipality within the so called 'Bible Belt'. Almost a quarter of the orthodox protestants is living outside this area.

In relation to tetanus, this less well vaccinated group does not pose a threat to other people, because tetanus is not transmitted between persons. Vaccinations results in individual protection. Herd immunity is not applicable for tetanus.

A study on the evolution of the vaccination coverage in this group shows that the coverage increases in subsequent generations with approximately 15% (4). The decision to vaccinate or not is mainly based on religious arguments, not on medical grounds (5).

Several other groups are also prone to have a lower vaccination coverage, e.g. people with a migration background or lower socio economic status (6). This is a problem in large cities, which needs special attention.

Which cut-off for protection should be used to assess the seroprevalence and what is the influence of cellular immunity?
Two cut-off's for seroprotection, i.e. 0.01 IU/mL and 0.1 IU/mL, are used. FDA uses the 0.1 IU/mL cut-off as the surrogate measure of the minimal protective level (7). In The Netherlands, we use both values to assess the seroprevalence against tetanus (2). For instance, the Health Council advised on tetanus post-exposure prophylaxis (T-PEP) (8). To inform the Health Council on this topic, De Melker et al. assessed the need to use Tetanus Immune Globulins (TIG) (9). Authors used both cut-off's as minimum and maximum level for seroprotection, respectively.

It is possible that, when large quantities of toxin are produced, a serum concentration of anti-tetanus antibody of 0.01 IU/mL or greater is insufficient to provide protection (7).

Active immunisation with TT containing vaccines confers immunity to tetanus by stimulating production of serum antibodies to tetanus toxin. Vaccination also induces cellular immunity for both T-cells and memory B-cells. Multiple tetanus immunisations lead to a sustained increase in numbers of TT-specific memory B cells (10). Memory B cell and antibody production are probably regulated independently (11).

T-lymphocytes are considered important targets for vaccines and antigen-specific helper T-cells play an essential role in priming TT-specific humoral and cellular responses Previously immunized, healthy adults have a robust T-cell response to TT booster immunisation, Memory responses for all T helper cells producing cytokines (TH1, Th2, Th17 and IL-10) were clearly identified (12, 13) Van der lee et al, unpublished results. These findings are somewhat questioning the practice of being re-immunized with TT every 10 years, at least, for enhancing the cellular T-helper response against tetanus.

However, cellular data for tetanus are still limited in relation to antibody data, although the order of magnitude of antibody persistence for at least two decades suggests re-evaluating the current recommendations for boosters, which may probably be delayed respect to the current 10-year interval. This recommendation has been proposed by other authors (14-18).

What is the impact of tetanus toxoid as a carrier protein in conjugated vaccines? Should elicited immune responses due to TT carrier proteins be counted as booster doses? What are possible consequences?
Conjugated vaccines are developed because children do not elicit an immune response to polysaccharide vaccines (19). After introduction of conjugated vaccines targeting *Haemophilus influenzae* type b, pneumococcal disease and meningococcal disease, also infants can be protected against these diseases. Tetanus toxoid, diphtheria toxoid or CRM197 (a genetically detoxified form of diphtheria toxin) are often used as a carrier protein. These carrier proteins also elicits a good immune response in children primed with TT of diphtheria vaccination and can act as a boosting dose (2, 20, 21). From a regulatory perspective, the booster immune response of carrier proteins is not taken into account for licensing the vaccine (personal communication Bettie Voordouw). Furthermore the type of carrier protein can change if a new European tender procedure results in a change of a specific vaccine. Such a change can lead to a changing number of booster doses, if the immune response to the carrier protein is counted as an official booster dose.

Lowering of the number of NIP booster doses or widening the interval between doses.

A minimum of two doses of standard-potency TT is considered necessary to reach minimal protective levels of antitoxin during the first year of life (7). Studies indicate that three doses may be needed before production of substantial antitoxin takes place and persists. This is also recommended by WHO (20). A RCT with varying primary series and boosters doses, performed in South Africa and Latin America, showed high protection up to 4.5 years after a booster dose in the second year of life: ≥99% and ≥76.8% had anti-TT ≥0.01 IU/mL and ≥0.1 IU/mL, respectively with GMTs in similar ranges in both study groups (22).

Serosurveillance of tetanus immunity assessed through the second Pienter survey, performed in 2006-2007, showed that 94.2% and 87.9% of the general Dutch population sample (n=6385) had anti-TT antibodies ≥ 0.01 IU/mL and ≥ 0.1 IU/mL, respectively, with a GMC of 0.91 IU/mL (figure 2) (2). Ninety three percent of this sample reported participation to the NIP. In the group, eligible for the NIP (born ≥1957), the percentage of people with anti-TT antibodies ≥ 0.01 IU/mL amounted to 99%. In contrast, seroprevalence among orthodox protestants who were eligible for the NIP was 36%, with 45% NIP participation. Orthodox protestants often refuse vaccination on religious grounds.

Age specific seroprevalence and GMC are presented in Figure 1. For people of 55 years of age and older the percentage of people with anti-TT antibody<0.01 IU/mL is increasing. This is the group that was not eligible for the NIP.
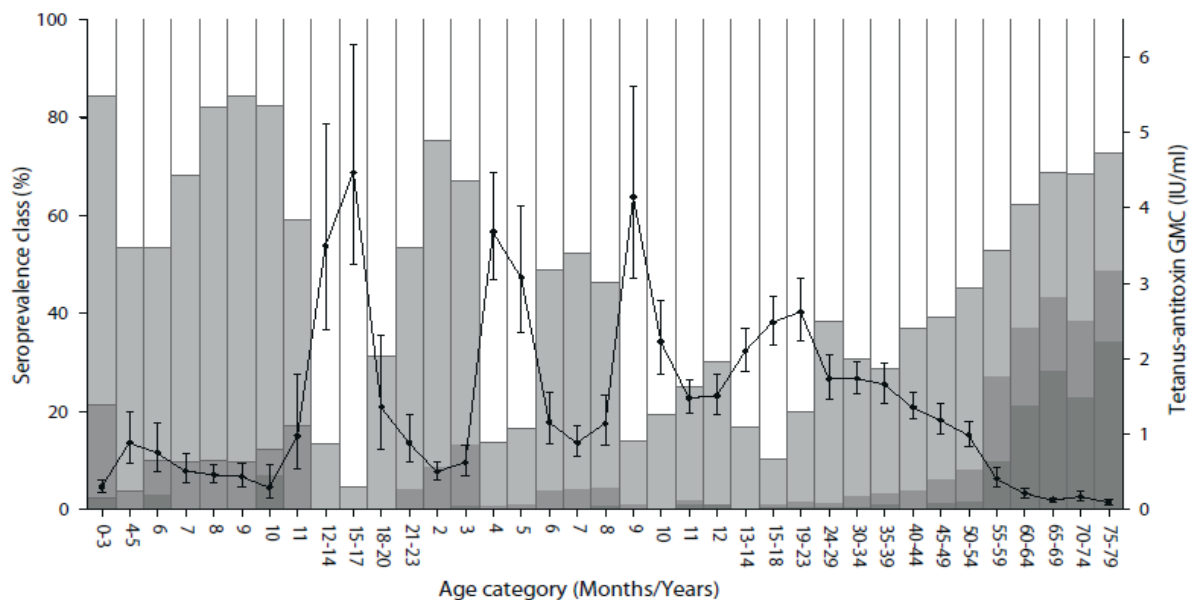
Figure 2 The columns represent the weighted age-group-specific seroprevalence of the general Dutch population. The dark grey column represents a TT antibody concentration <0.01 IU/mL; the grey column represents a concentration ≥0.01 IU/mL and <0.1 IU/mL.; the light grey column represents ≥0.1 IU/mL and <1.0 IU/mL and the white column represents ≥1.0 IU/mL. the black line indicated the weighted age-group-specific TT antibody GMC (IU/mL). The error bars show the 95%CI.

The total number of TT-doses (including the TT carrier protein in conjugated vaccines) within the NIP is somewhat higher than the 6 doses, advised by WHO (20). The intervals between the TT-containing vaccinations in the Dutch NIP is in line with the WHO advice. However, based on the 2 consecutive Pienter seroprevalence studies (see description above), the booster dose at 4 years of age could be left out. As an alternative, the interval of TT boosting (i.e. if the last TT vaccination is >10y ago) may be widened.

The necessity of booster doses at adult age is uncertain
As already described the overall seroprotection of the general population in The Netherlands is good with only low seroprevalence rates in people from 55 years of age onwards.

From December 2019 onwards, expectant mothers can receive a dTap vaccination to protect the newborn against pertussis. This is also a booster dose in previously vaccinated women. Vaccination coverage of the maternal Tdap is 70% (23).

In studies conducted in high income countries where infant immunisation starts around two months of age, an acceptable immune response is achieved after booster doses of TT even when intervals of longer than 20 years have elapsed since the last dose, although the briskness and height of response and duration of protective antitoxin levels are somewhat dependent on the length of time since the primary vaccination (7, 20). Many countries recommend booster TT doses every 10 years. This is also true for the majority of European countries (24). However, the need for this is questioned because 1. Several serosurveys, including the Pienter survey performed in The Netherlands, have supported duration of protective immunity for at least 20 years, if not substantially longer and 2. Fewer cases of tetanus and even fewer associated deaths are reported among people who received a primary series, irrespective of receiving booster doses.

A Portuguese study also indicated there is no need for decennial TT booster doses (17). Hundred women (mean age 57.8y; range 29.8y-97.5y) received Td vaccination. Twenty two women started DT immunisation during childhood, 66 received only TT during adolescence or adulthood. At adult age, anti-TT concentrations were above threshold and vaccination resulted in good immune responses in both groups.

The necessity of an update of the T-PEP guideline
On top of the data, described in the previous section, many adult people receive additional TT booster doses for traveling or as post exposure prophylaxis (T-PEP).

In relation to the use of TIG as part of T-PEP, the adherence to the Health Council guideline (8) can be improved. A Dutch study showed underuse of TIG (1). In contrast, TT is overused. Perhaps the use of a bedside test to assess tetanus immunity with 20 minutes can have added value. These rapid tests use 0.1 IU/mL as cut-off and report sensitivities of 55%-100% and very high specificity compared with ELISA results (7). Validations using in vivo neutralization assays as golden standard showed much lower specificities. In France, these tests

were found to be cost-effective compared with medical interviews for patients with tetanus-prone wounds (25). Furthermore, based on the 2 consecutive Pienter seroprevalence studies, performed in 1995-1996 and 2006-2007, the interval of TT boosting (i.e. if the last TT vaccination is >10y ago) may be widened.

In the Dutch serosurvey, performed in 2006-2007, 61% of the national sample (n=6385) were eligible for T-PEP, according to current guidelines (2). Of these, 34% were born before start of the NIP, 70% did not have sufficient registered TT vaccinations and 35% received their last TT booster dose >10 years earlier. Of this national sample, 34% reported having sustained a wound in the month before study participation but only 2.6% received T-PEP. Of the 97.4% who did not receive T-PEP, 10% had a antitoxin concentration <0.01IU/mL, while 81% had a concentration >0.1IU/mL. A regression analysis predicted that protective antibody levels would persist until 90 years of age, with a GMT of 0.22 IU/mL (2, 20). Several other studies suggested persisting protective immunity for 20-30 years after a sixth dose of TT containing vaccines (20).

Similar conclusions were drawn from a study that assessed the added value of a bedside test to quickly measure tetanus immunity among adults attending the emergency department with a wound (1). The study showed that, according to the bedside test 73% of the participants born from 1957 onwards and therefore eligible for the NIP were sufficiently protected and did not need T-PEP although they were in the running for this according to the Dutch T-PEP guideline. For the group born before 1957, this percentage was 36%. In contrast, 8% (born ≥1957) and 22% (born <1957) were not protected according to the bedside test, but did not qualify for T-PEP according to the national guideline.

The need for TT booster doses in relation to T-PEP and if necessary the interval between the doses could be part of an update of the T-PEP guideline of the Health Council.

3.3.6   *Conclusions and suggestions for the request for advice from the Health Council*
The protection against tetanus induced by vaccination is longlasting, even though the precise determinants for protection are not known. The current vaccination schedule may include more immunisations than needed at too short intervals. Thus, the number of immunisations may be reduced or the intervals between doses may be increased. The use of tetanus antigen as a carrier protein for other vaccines most likely adds to the immunity against tetanus and a relevant question is whether and how such use could be taken into account. The adherence to the T-PEP guideline regarding the use of TIG could be improved. Furthermore, the need for and interval between TT booster doses in the T-PEP guideline needs updating.

3.3.7 References

1. van der Maas NA, Donken R, Te Wierik MJ, Swaan CM, Hahne SJ, de Melker HE. Performance of a bedside test for tetanus immunity: results of a cross-sectional study among three EDs in the Netherlands in 2012-2013. Emerg Med J. 2016.

2. Steens A, Mollema L, Berbers GA, van Gageldonk PG, van der Klis FR, de Melker HE. High tetanus antitoxin antibody concentrations in the Netherlands: a seroepidemiological study. Vaccine. 2010;28(49):7803-9.

3. Ruijs WL, Hautvast JL, van der Velden K, de Vos S, Knippenberg H, Hulscher ME. Religious subgroups influencing vaccination coverage in the Dutch Bible belt: an ecological study. BMC Public Health. 2011;11:102.

4. Spaan DH, Ruijs WL, Hautvast JL, Tostmann A. Increase in vaccination coverage between subsequent generations of orthodox Protestants in The Netherlands. European journal of public health. 2017.

5. Ruijs WL, Hautvast JL, van Ijzendoorn G, van Ansem WJ, van der Velden K, Hulscher ME. How orthodox protestant parents decide on the vaccination of their children: a qualitative study. BMC Public Health. 2012;12:408.

6. van Lier A, van de Kassteele J, de Hoogh P, Drijfhout I, de Melker H. Vaccine uptake determinants in The Netherlands. European journal of public health. 2013.

7. Plotkin S, Orenstein WA, Offit PA. Vaccines. 7 ed2018.

8. Gezondheidsraad. Immunisatie tegen tetanus bij verwonding. den Haag; 2003. Report No.: 2003/11.

9. de Melker HE, Steyerberg EW. [Function of tetanus immunoglobulin in case of injury: administration often unnecessary]. Ned Tijdschr Geneeskd. 2004;148(9):429-33.

10. van der Lee S, van Rooijen DM, de Zeeuw-Brouwer ML, Bogaard MJM, van Gageldonk PGM, Marinovic AB, et al. Robust Humoral and Cellular Immune Responses to Pertussis in Adults After a First Acellular Booster Vaccination. Front Immunol. 2018;9:681.

11. Amanna IJ, Carlson NE, Slifka MK. Duration of humoral immunity to common viral and vaccine antigens. N Engl J Med. 2007;357(19):1903-15.

12. Cellerai C, Harari A, Vallelian F, Boyman O, Pantaleo G. Functional and phenotypic characterization of tetanus toxoid-specific human CD4+ T cells following re-immunization. Eur J Immunol. 2007;37(4):1129-38.

13. Livingston KA, Jiang X, Stephensen CB. CD4 T-helper cell cytokine phenotypes and antibody response following tetanus toxoid booster immunization. J Immunol Methods. 2013;390(1-2):18-29.

14. Ferlito C, Biselli R, Mariotti S, von Hunolstein C, Teloni R, Ralli L, et al. Tetanus-diphtheria vaccination in adults: the long-term persistence of antibodies is not dependent on polyclonal B-cell activation and the defective response to diphtheria toxoid re-vaccination is associated to HLADRB1 *01. Vaccine. 2018;36(45):6718-25.

15. Hammarlund E, Thomas A, Poore EA, Amanna IJ, Rynko AE, Mori M, et al. Durability of Vaccine-Induced Immunity Against Tetanus and Diphtheria Toxins: A Cross-sectional Analysis. Clin Infect Dis. 2016;62(9):1111-8.
16. Scheibel I. The uses and results of active tetanus immunization. Bull World Health Organ. 1955;13(3):381-94.
17. Goncalves G, Santos MA, Frade JG, Cunha JS. Levels of diphtheria and tetanus specific IgG of Portuguese adult women, before and after vaccination with adult type Td. Duration of immunity following vaccination. BMC Public Health. 2007;7:109.
18. Gardner P, LaForce FM. Protection against tetanus. N Engl J Med. 1995;333(9):599-600.
19. Barrett DJ. Human immune responses to polysaccharide antigens: an analysis of bacterial polysaccharide vaccines in infants. Adv Pediatr. 1985;32:139-58.
20. Tetanus vaccines: WHO position paper - February 2017. Wkly Epidemiol Rec. 2017;92(6):53-76.
21. de Voer RM, Mollema L, Schepp RM, de Greeff SC, van Gageldonk PG, de Melker HE, et al. Immunity against Neisseria meningitidis serogroup C in the Dutch population before and after introduction of the meningococcal c conjugate vaccine. PLoS One. 2010;5(8):e12144.
22. Madhi SA, Lopez P, Zambrano B, Jordanov E, B'Chir S, Noriega F, et al. Antibody persistence in pre-school children after hexavalent vaccine infant primary and booster administration. Hum Vaccin Immunother. 2019;15(3):658-68.
23. van Lier A, Oomen P, Giesbers H, van Vliet H, Hament J-M, Drijfhout I, et al. Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2020. Bilthoven: RIVM; 2021.
24. Weinberger B. Adult vaccination against tetanus and diphtheria: the European perspective. Clin Exp Immunol. 2017;187(1):93-9.
25. Yen LM, Thwaites CL. Tetanus. Lancet. 2019;393(10181):1657-68.

3.4 Poliomyelitis

3.4.1 History of vaccination against poliomyelitis

Trivalent inactivated poliomyelitis vaccination (IPV) has been used in The Netherlands from the start of the NIP in 1957. In the current Dutch NIP, infants and children receive five or six IPV containing vaccinations, depending whether the mother received a maternal Tdap vaccination during pregnancy. In this NIP schedule, IPV is part of a hexavalent DTaP-IPV-Hib-HepB vaccine for infants (3 or 4 doses), a dTap-IPV booster dose for 4-year-olds and a dT-IPV booster dose at 9 years of age.

3.4.2 Goal of vaccination against poliomyelitis

The main goal of vaccination against poliomyelitis is the prevention of disease among all ages, because poliomyelitis can lead to death, permanent disabling sequelae or severe disease requiring hospitalization. In the light of this first goal, remaining the polio-free status in the European region and eradication of all three types of poliovirus are important goals too (1).

3.4.3   *Epidemiology of polio in The Netherlands*
In The Netherlands, the last outbreak of poliomyelitis occurred in 1992-
1993 with 71 WPV3 cases, including two deaths (figure 1). All cases
were unvaccinated and adhered the orthodox protestant community.
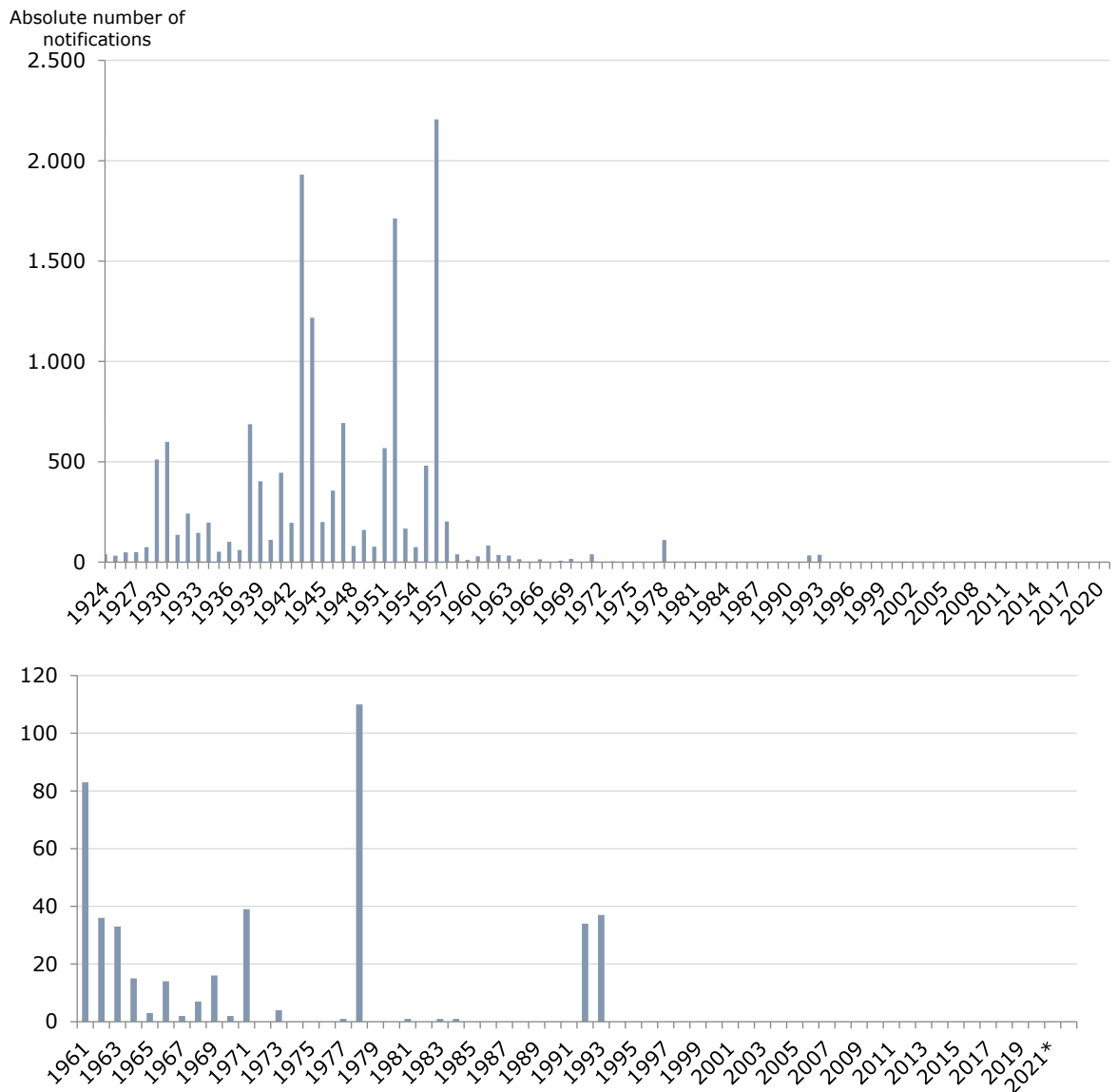
Figure 1 Notifications of poliomyelitis in The Netherlands from 1924-2021 (top
part) and zoomed in * (bottom part) on 1961-2021*
*for 2021, reports up to and including August 31th were included

3.4.4   *Assessment of the vaccination against the six criteria, issues identified*
Criterion 1. Is the protection adequate for all those intended to be
protected?
Immunosurveillance shows high neutralizing anti-poliovirus antibodies in
the national sample with slow waning of humoral immunity. However,
seroprevalence in orthodox protestants communities is much lower. Due
to this socio-geographically clustered community, (re)introduction or
silent circulation of poliovirus is possible, because only approximately
1% of infected people show signs of clinical poliomyelitis. To detect this

as soon as possible, besides mandatory notification of a possible case of poliomyelitis, other surveillance pillars with high sensitivity should be in place.

Furthermore, cellular immunity plays an important role in protection of people with undetectable antibodies.

Issues related to criterion 1
- The protection of orthodox protestant people that reject vaccination, is low.
- The level of the poliovirus surveillance system that is appropriate for The Netherlands should be discussed.

Criterion 2. Is the applied vaccination strategy optimal?
From the start of the NIP, vaccination coverage of vaccines targeting poliomyelitis has been continually high in The Netherlands. The European region is certified as polio free since 2002. The last polio outbreak in The Netherlands occurred in 1992-1993. These data suggest that the applied vaccination strategy against poliomyelitis works well. In relation to the GAPIII eradication plan, IPV based on attenuated Sabin virus strains (sIPV) is being developed and will likely be advised in near future.

Issues related to criterion 2
- Change from standard IPV to sIPV should be discussed.

Criterion 3. Does the programme include too much?
A series of three doses of IPV vaccine is sufficient to protect infants and children against paralytic disease. There is no evidence that protective immunity against paralytic disease wanes over time. The possible impact of a three dose schedule on infection and transmission is uncertain. The current NIP includes 5 or 6 IPV containing vaccinations, depending whether the infant's mothers received a Tdap vaccination during pregnancy. This is probably more than needed.

Issues related to criterion 3
- The number of NIP booster doses could be reduced.

Criterion 4. Does the programme include too little?
No, there is no evidence that the programme has insufficient impact.

Criterion 5. Is the timing of immunisations using combination vaccines optimal or at least acceptable?

A series of three infant doses of IPV vaccine is sufficient for protection against paralytic disease as soon as possible. There is no evidence that protective immunity against paralytic disease wanes over time. The timing of booster doses is flexible.

Issues in relation to criterion 5
- Spreading the IPV booster doses could further prolong the high anti-poliovirus seroprevalence.

Criterion 6. Are there important drawbacks of the NIP? For the population as a whole? For those who opt out? How are these drawbacks to be weighed against the advantage of the programme and its components?

No important drawbacks in relation to the public vaccination programme against poliomyelitis are known.

3.4.5   *Exploration of the issues against available evidence*

The protection of orthodox protestant people is low

Anti-Poliovirus seroprevalence among the general population, assessed in 2006-2007, was 94.6% (type 1), 91.8% (type 2) and 84.0% (type 3). In contrast, among orthodox protestants seroprevalence was 64.9% (type 1), 61.0% (type 2) and 62.1% (type 3) (2). The age specific seroprevalence rates in this the sample of low vaccination coverage (LVC) municipalities clearly reflected the influence of poliomyelitis outbreaks in the past.

It is a well-known fact that The Netherlands includes a groups of socio-geographically clustered people who refuse vaccination on religious grounds. This group comprises approximately 220,000 members (i.e. 1.3% of the Dutch population; reference date 1-1-2006) (3). About three quarter live in a municipality within the so called 'Bible Belt'. Almost a quarter of the orthodox protestants is living outside this area. A study on the evolution of the vaccination coverage in this group shows that the coverage increases in subsequent generations with approximately 15% (4). The decision to vaccinate or not is mainly based on religious arguments, not on medical grounds (5).

The existence of this socio-geographically clustered community, is one argument the European Regional Certification Commission for poliovirus eradication (RCC) used to assess the risk of transmission following importation of wild type virus (WPV) or vaccine-derived polio virus (VDPV) in The Netherlands as intermediate.

Several other groups are also prone to have a lower vaccination coverage, e.g. people with a migration background or lower socio economic status (6). This is a problem in large cities, which needs special attention.

The level of the currently used surveillance system should be discussed

Another argument for the RCC to determine the risk of transmission as intermediate is the presence of several poliovirus facilities in The Netherlands and neighboring countries. This aspect is illustrated by several spills in recent years. For instance, in April 2017, a WPV2 spill occurred in a Dutch vaccine manufacturing plant (7). Two fully vaccinated operators with risk of exposure were advised on maintaining stringent personal hygiene and were monitored for virus shedding. Poliovirus (WPV2-MEF1) was detected in the stool of one, 4 days after exposure, and later also in sewage samples. The operator was isolated at home and was followed up until shedding stopped 29 days after exposure. No further transmission was detected. Likewise, following a vaccine trial in Belgium in May 2017, five Dutch participants were allowed to leave containment and return to The Netherlands without proof of having stopped shedding the new Oral Polio Vaccine type 2

virus (8). One of the participants continued shedding for 24 days while living in The Netherlands. No transmission to others occurred. Most recently, during routine environmental surveillance at the premises of the poliovirus essential facilities in The Netherlands, a poliovirus was isolated from a sewage sample of July 21, 2020. After whole genome sequencing the isolated strain proved to be a poliovirus wildtype 3 strain, with 4 mutations relative to the Saukett G strain as used for the production of inactivated polio vaccine. The identification of 1 person with a PV3 specific antibody titer increase, and the absence of the strain with 4 SNPs in the vaccine seed stocks or produced batches, lead to the conclusion that infection and shedding of WPV3 Saukett by this person is the most likely reason for detection of WPV3 in the sewage. This person lives alone in an >92% vaccination coverage area.

In a sample form the same sampling site collected October 12, 2021 a WPV1- Mahoney (IPV strain) was isolated with a single mutation. The same mutation was found in the harvest of the vaccine production from that period. In none of the employees studied by feces and serum analysis a sign of recent poliovirus infection was found. In the routine enterovirus surveillance, based on both clinical and environmental enterovirus surveillance, as performed in The Netherlands to early detect poliovirus introduction, no poliovirus was detected.

In The Netherlands, early detection of poliovirus is based on environmental enterovirus surveillance (9) and clinical enterovirus surveillance. Furthermore, polio is a group A notifiable disease.

In case of an introduction of poliovirus or the spread of silent WPV/VDPV, the situation in The Netherlands may very much resemble the situation that occurred in Israel in 2013 (10). At that moment, Israel suffered from a silent WPV1 importation and sustained transmission. With the aim of preventing clinical poliomyelitis and ensuring virus re-elimination, the authorities intensified the clinical and environmental surveillance activities and enhanced vaccination coverage. No paralytic polio case was detected. With the current level of polio- and enterovirus surveillance in The Netherlands, experts state that silent spread should be picked up at an early stage and paralytic cases could be prevented (9). Vaccination to stop the outbreak probably can be restricted to communities of orthodox protestant people with low vaccination coverage, because in the general population vaccination coverage has been high continually. Such a tailored vaccination offer was also given during the last outbreaks of poliomyelitis in The Netherlands (11).

Change from standard IPV to sIPV should be discussed
For protection against poliomyelitis, Oral Polio Vaccine (OPV; developed by Sabin) and Inactivated Polio Vaccine (IPV; developed by Salk) are available. In the light of polio eradication, WHO urges all countries to incorporate at least 1 IPV-dose in the vaccination schedule (1). Eventually, only IPV should be used. Furthermore, in the near future, use of sIPV based on Sabin virus strains (sIPV) will be advised because Sabin strains are much safer to work with in the production process than the WPV strains in the current Salk IPV. It is foreseeable that this will further shift to the use of S19-Sabin strains (hyper attenuated Sabin strains, developed to prevent reversion to pathogenicity, thus

preventing vaccine-derived polio) since for these strains biocontainment requirements are less stringent than for WPV or Sabin strains (12) (13).

Lowering of the number of NIP booster doses or widening the interval between doses

As already mentioned, a 2+1 IPV vaccination series confers good and long-lasting protection against paralytic disease (14). However, immunity to paralysis does not prevent individuals from getting infected and potentially participating in poliovirus transmission. Very limited data exist to directly support quantification of model inputs related to transmission. Therefore, there is a need for additional studies. Despite the uncertainties described above, the current number of 5 or 6 IPV doses is probably higher than necessary.

Likewise, the Pienter 2 serosurveillance data showed that people with a completed NIP vaccination series and no booster doses later in life still had protective antibody titres against all three serotypes at 40 years of age (Figure 2; non-protection <3) (2). However, during this study, NIP contained 5 IPV doses.
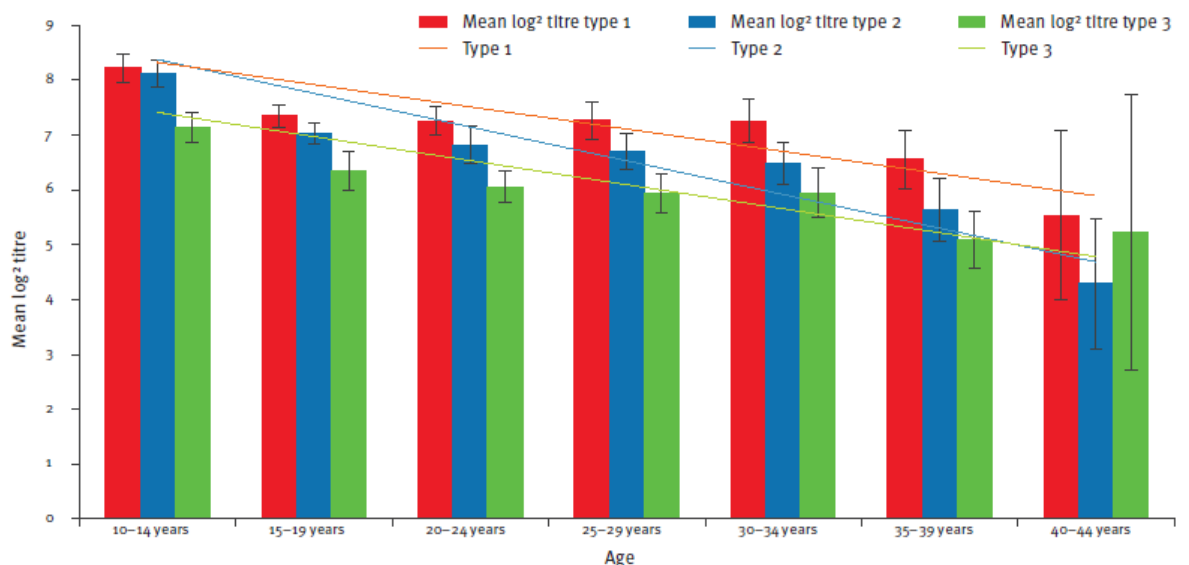
Figure 2 Poliovirus mean log2 titres in 10-44 year-olds in the nationwide sample who completed the NIP vaccination series with no revaccinations, stratified by age, The Netherlands, 2006-2007 (n=1260) (2).

On the other hand, the risk analysis performed in the Pienter 2 seroprevalence study suggested that individuals who had received their last IPV-containing vaccination more than 20 years before sampling, were at increased risk of having antibody titres below the protective threshold (Table 1). In this risk analysis, however, good cellular protection of people without detectable antibodies was not taken into account (15). Therefore, as an alternative to reducing the number of vaccination doses, better spreading IPV doses throughout the entire period of NIP eligibility, i.e. till the age of 18 years, might have a positive impact on the duration of protection.

Table 1 Multivariable logistic regression analysis of risk factors for non-protection against poliovirus types 1, 2 and 3 in the nationwide sample, The Netherlands, 2006-2007 (n=6386).

Demographic- or vaccination-related factor	Sub-category	Total, *n*	Poliovirus type1		Poliovirus type2		Poliovirus type3	
			NT <3, %	Adjusted OR (95% CI)	NT <3, %	Adjusted OR (95% CI)	NT <3, %	Adjusted OR (95% CI)
Sex	Male	2912	6.3	ref	8.8	ref	16.7	Ref
	Female	3474	5.6	0.93 (0.75-1.16)	8.2	0.92 (0.76-1.11)	15.2	0.90 (0.78-1.04)
Age in years	0	348	19.3	ref	19.3	ref	21.8	ref
	1-apr	514	5.3	**0.22 (0.12-0.40)**	6.0	**0.35 (0.19-0.64)**	23.5	0.69 (0.44-1.08)
	5-sep	620	1.8	**0.09 (0.04-0.20)**	1.3	**0.09 (0.04-0.21)**	12.3	**0.33 (0.20-0.55)**
	okt-19	730	1.9	**0.14 (0.06-0.37)**	1.9	**0.11 (0.04-0.26)**	7.8	**0.18 (0.10-0.32)**
	20-29	712	1.1	**0.06 (0.03-0.15)**	1.8	**0.06 (0.02-0.13)**	7.9	**0.12 (0.07-0.22)**
	30-39	715	3.4	**0.07 (0.03-0.16)**	4.8	**0.06 (0.03-0.13)**	13.2	**0.16 (0.09-0.28)**
	40-49	641	7.6	**0.08 (0.04-0.17)**	13.1	**0.12 (0.06-0.24)**	23.1	**0.17 (0.10-0.30)**
	50-59	714	7.8	**0.09 (0.04-0.18)**	8.7	**0.08 (0.04-0.16)**	18.6	**0.14 (0.08-0.25)**
	60-69	799	7.5	**0.09 (0.04-0.18)**	15.0	**0.16 (0.08-0.31)**	16.4	**0.13 (0.07-0.22)**
	70-79	593	10.1	**0.11 (0.05-0.23)**	17.9	**0.18 (0.09-0.35)**	20.4	**0.15 (0.09-0.26)**
Geographic region	Northeast	1505	6.6	ref	9.1	ref	16.0	ref
	Central	1122	7.1	1.06 (0.69-1.63)	9.9	1.06 (0.72-1.55)	16.3	0.97 (0.72-1.31)
	Northwest	1527	5.1	0.93 (0.67-1.30)	7.0	0.91 (0.68-1.21)	14.7	1.03 (0.83-1.27)
	Southwest	1125	5.0	**0.62 (0.42-0.92)**	8.0	0.82 (0.59-1.15)	15.9	0.93 (0.72-1.19)
	Southeast	1107	5.7	0.83-0.58-1.19)	8.5	0.87 (0.64-1.19)	16.8	1.05 (0.83-1.33)
Degree of urbanization	Very high	1399	5.2	ref	6.5	ref	14.4	ref
	High	2848	6.1	0.86 (0.62-1.19)	8.3	1.06 (0.79-1.41)	15.5	0.92 (0.75-1.13)
	Moderately high	804	6.0	0.74 (0.49-1.13)	10.3	1.20 (0.85-1.70)	18.7	1.04 (0.81-1.35)
	Low	589	7.3	0.79 (0.46-1.36)	10.3	1.07 (0.66-1.74)	16.3	0.87 (0.60-1.27)
	Very low	746	5.4	0.63 (0.40-1.00)	9.1	0.99 (0.66-1.48)	16.5	0.89 (0.66-1.19)
Migrant status	Dutch citizens and Western immigrants	5317	6.6	ref	9.5	ref	17.3	ref

Demographic- or vaccination-related factor	Sub-category	Total, n	Poliovirus type1		Poliovirus type2		Poliovirus type3	
			NT <3, %	Adjusted OR (95% CI)	NT <3, %	Adjusted OR (95% CI)	NT <3, %	Adjusted OR (95% CI)
	Non-Western immigrants	1069	2.4	**0.42 (0.26-0.67)**	3.0	**0.47 (0.31-0.71)**	8.7	**0.47 (0.35-0.62)**
Educational level[a]	Low	730	4.3	ref	7.5	ref	12.3	ref
	Mid	3138	6.4	**1.57 (1.03-2.40)**	10.0	**1.48 (1.06-2.08)**	16.0	1.21 (0.93-1.57)
	High	2403	5.9	**1.70 (1.09-2.67)**	6.8	1.26 (0.87-1.82)	16.8	**1.51 (1.14-2.00)**
	Unknown	115	1.7	0.51 (0.12-2.20)	7.0	1.25 (0.55-2.82)	13.9	1.23 (0.68-2.24)
Extent of vaccination refusal according to religious views	None or minor	5317	6.6	ref	8.3	ref	15.6	ref
	Moderate to strong	133	15.0	**2.86 (1.66-4.91)**	16.5	**1.97 (1.17-3.31)**	27.1	**1.79 (1.18-2.72)**
Duration in years between last polio-containing vaccination and blood sampling	0	503	10.7	ref	11.1	ref	12.9	ref
	1-mrt	1201	3.3	1.46 (0.80-2.69)	3.3	1.16 (0.64-2.10)	13.6	**2.86 (1.84-4.44)**
	4-sep	946	1.6	1.60 (0.68-3.77)	1.1	0.80 (0.32-1.99)	8.0	**3.69 (2.17-6.26)**
	okt-20	735	0.1	0.19 (0.02-1.54)	1.1	0.96 (0.36-2.57)	7.8	**5.25 (2.93-9.39)**
	21-30	407	3.0	**4.47 (1.70-11.78)**	6.1	**5.97 (2.59-26.58)**	12.0	**7.24 (3.87-13.52)**
	>31	264	11.0	**9.31 (4.13-21.00)**	17.1	**12.54 (5.92-26.58)**	31.8	**18.75 (10.42-33.74)**
	Unknown	103	1.0	0.48 (0.06-3.84)	1.9	0.83 (0.19-3.76)	13.6	4.38 (2.11-9.12)
	Not vaccinated	2227	10.1	**13.58 (5.09-36.24)**	15.9	**5.28 (2.46-11.31)**	22.7	**21.44 (11.18-41.10)**
Number of polio-antigen containing vaccinations	6 (completed NIP)	1498	1.3	ref	2.6	ref	8.6	ref
	0-1	2592	9.0	1.29 (0.47-3.55)	14.5	1.95 (0.99-3.85)	20.3	0.85 (0.49-1.47)
	2-mei	1900	6.3	**2.63 (1.31-5.28)**	6.2	1.04 (0.61-1.80)	17.6	**1.61 (1.15-2.26)**
	6, including single IPV or OPV	68	4.4	1.86 (0.47-7.31)	4.4	0.48 (0.13-1.74)	16.2	1.19 (0.56-2.53)
	≥7	328	0.6	0.61 (0.14-2.75)	1.5	0.67 (0.25-1.81)	4.0	0.59 (0.32-1.10)
Travelling to high-risk regions[b]	No	3956	7.7	ref	11.5	ref	20.0	ref
	Yes	2430	2.9	**0.61 (0.46-0.82)**	3.5	**0.44 (0.34-0.58)**	9.1	**0.57 (0.47-0.68)**

3.4.6   *Conclusion and suggestions for the request for advice from the Health Council*

Polio vaccination is highly effective and the strategy of universal vaccination works well. The level of risk of transmission following importation of wild type virus (WPV) or vaccine-derived polio virus (VDPV) in The Netherlands was assessed as intermediate for two reasons: 1) the low level of protection in some orthodox protestant communities, even though it is improving over time, and 2) the presence of facilities in the country where infective wild polio virus is processed. Both risks necessitate permanent attention for the appropriate level of poliovirus surveillance. A primary series of two doses and one booster dose confers good and long-lasting protection against paralytic disease. The current 0 to 9 years vaccination schedule with five doses IPV is probably more than necessary and may better be changed to a 0 to 18 years schedule including four doses instead. The impact of such a change on infection and transmission is uncertain, but with adequate surveillance in place a possible outbreak can be detected quickly and contained via targeted vaccination. The change to using IPV based on attenuated Sabin virus strains (sIPV) instead of standard IPV should be discussed.

3.4.7   *References*

1.   Polio vaccines: WHO position paper - March, 2016. Wkly Epidemiol Rec. 2016;91(12):145-68.
2.   van der Maas N, Mollema L, Berbers G, van Rooijen D, van der Avoort H, Conyn-Van Spaendonck M, et al. Immunity against poliomyelitis in the Netherlands, assessed in 2006 to 2007: the importance of completing a vaccination series. Euro Surveill. 2014;19(7).
3.   Ruijs WL, Hautvast JL, van der Velden K, de Vos S, Knippenberg H, Hulscher ME. Religious subgroups influencing vaccination coverage in the Dutch Bible belt: an ecological study. BMC public health. 2011;11:102.
4.   Spaan DH, Ruijs WL, Hautvast JL, Tostmann A. Increase in vaccination coverage between subsequent generations of orthodox Protestants in The Netherlands. Eur J Public Health. 2017.
5.   Ruijs WL, Hautvast JL, van Ijzendoorn G, van Ansem WJ, van der Velden K, Hulscher ME. How orthodox protestant parents decide on the vaccination of their children: a qualitative study. BMC public health. 2012;12:408.
6.   van Lier A, van de Kassteele J, de Hoogh P, Drijfhout I, de Melker H. Vaccine uptake determinants in The Netherlands. Eur J Public Health. 2013.
7.   Duizer E, Ruijs WL, van der Weijden CP, Timen A. Response to a wild poliovirus type 2 (WPV2)-shedding event following accidental exposure to WPV2, the Netherlands, April 2017. Euro Surveill. 2017;22(21).
8.   Schurink-van 't Klooster TM, De Melker HE. The National Immunisation Programme in the Netherlands; surveillance and developments in 2017-2018. Bilthoven: National Institute for Public Health and the Environment; 2018.

9.   Benschop KSM, van der Avoort HG, Jusic E, Vennema H, van Binnendijk R, Duizer E. Polio and measles down the drain: Environmental Enterovirus Surveillance in the Netherlands, 2005-2015. Appl Environ Microbiol. 2017.

10.   Kaliner E, Kopel E, Anis E, Mendelson E, Moran-Gilad J, Shulman LM, et al. The Israeli public health response to wild poliovirus importation. Lancet Infect Dis. 2015;15(10):1236-42.

11.   Oostvogel PM, van Wijngaarden JK, van der Avoort HG, Mulders MN, Conyn-van Spaendonck MA, Rumke HC, et al. Poliomyelitis outbreak in an unvaccinated community in The Netherlands, 1992-93. Lancet. 1994;344(8923):665-70.

12.   Knowlson S, Burlison J, Giles E, Fox H, Macadam AJ, Minor PD. New Strains Intended for the Production of Inactivated Polio Vaccine at Low-Containment After Eradication. PLoS Pathog. 2015;11(12):e1005316.

13.   Plotkin S, Orenstein WA, Offit PA. Vaccines. 7 ed2018.

14.   Duintjer Tebbens RJ, Pallansch MA, Chumakov KM, Halsey NA, Hovi T, Minor PD, et al. Expert Review on Poliovirus Immunity and Transmission. Risk Anal. 2012.

15.   Abbink F, Buisman AM, Doornbos G, Woldman J, Kimman TG, Conyn-van Spaendonck MA. Poliovirus-specific memory immunity in seronegative elderly people does not protect against virus excretion. J Infect Dis. 2005;191(6):990-9.

3.5   Vaccination against hepatitis B

3.5.1   History of vaccination against hepatitis B

In The Netherlands, targeted vaccination against hepatitis B has been in place for behavioural risk groups, patient risk groups and medical personnel from 1983. In 1989 screening of pregnant women for hepatitis B surface antigen (HBsAg) to detect chronic HBV infection, and subsequent vaccination of infants born to mothers with chronic HBV infection was implemented. Since 2002 the hepatitis B vaccination programme for behavioral risk groups has included men having sex with men (MSM), heterosexulas with multiple partners (until 2007), sex workers, and drug users (until 2012). Hepatitis B immunisation (active and passive) is also part of post-exposure prophylaxis (PEP) regimens after risk of transmission due to blood-blood contact or sex-accidents.

In the period 2003-2011 children with at least one parent born in a country with intermediate to high HBsAg prevalence were offered vaccination as part of the NIP. Since 2011 the NIP includes hepatitis B vaccination for all infants, currently as DtaP-IPVHepBHib at 3, 5, and 11 months of age. Additionally, infants of HBsAg positive mothers receive immunoglobulin (HBIg) and a dose of single hepatitis B vaccine at birth and an extra dose of DtaP-IPVHepBHib combination vaccine at 2 months of age.

3.5.2   Goal of vaccination against hepatitis B

The main goal of vaccination against hepatitis B is to prevent hepatitis B (acute and chronic) and its long-term sequelae. A second goal is to reach elimination in the WHO European region by 2030.

3.5.3   *Epidemiology of hepatitis B in The Netherlands*
Since the 1980s, there has been a downward trend in the incidence of acute hepatitis B virus (HBV) infection in The Netherlands (Figure 1). In recent years (2018-2020), around 100 cases of acute HBV infections were reported annualy. In this period the vast majority (80-90%) of cases were in the age group 20-59 years. The incidence of acute HBV infection is higher in men than in women, with around three quarters of the notifications in men in the past 10 years. The most reported route of transmission for acute HBV infection is sexual contact (around 60% in 2018-2020).

Chronic hepatitis B virus infection has been notifiable since the year 2000. The number of newly diagnosed chronic infections per year increased from about 1,200 in 2000 to over 1,800 in 2009. Since 2013 the number of newly diagnosed chronic infections decreased to around 1,000-1,100 annualy, corresponding to an incidence of around 6 per 100,000 population (Figure 1). The vast majority of patients with a chronic HBV infection were born abroad (around 90% in 2018-2020). In 2020 the number of new diagnoses declined to 714 cases, which likely reflects missed opportunities for diagnosis due to a reduction in health seeking behaviour during the COVID-19 pandemic.[1]
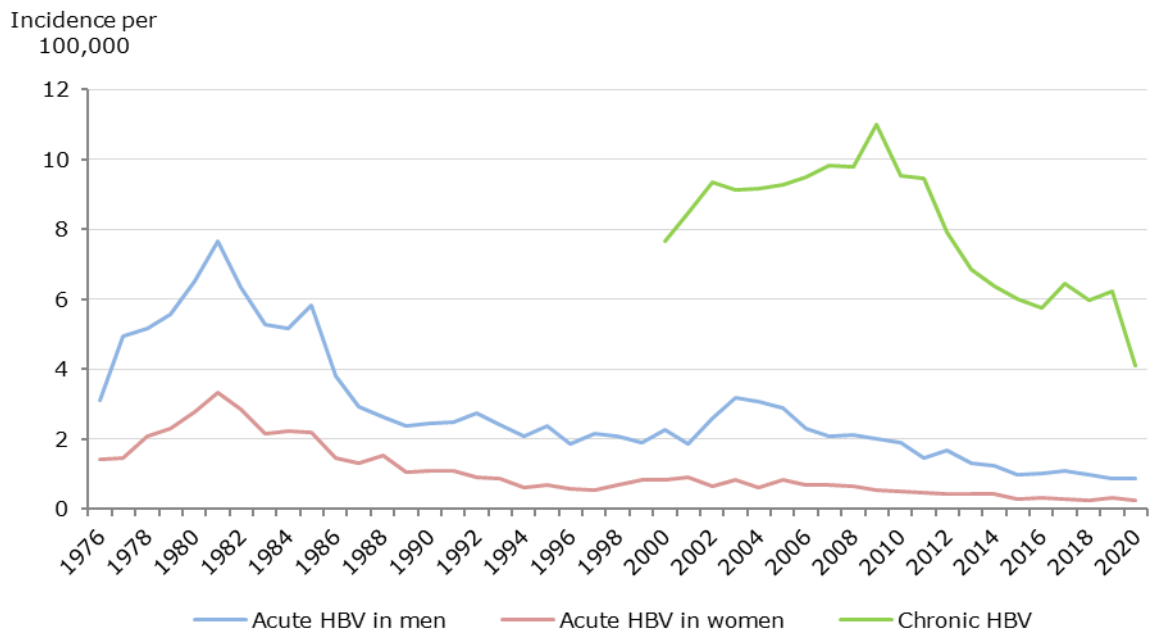

Figure 1 Annual incidence of reported acute and chronic hepatitis B cases since 1976.

The prevalence of chronic HBV infection in The Netherlands was estimated to be 0.34% (0.22-0.47%) in 2016, which corresponds to approximately 49,000 persons with a chronic infection.[2] An estimated 81% of them are first-generation migrants.

Fulminant liver failure after acute HBV infection is rare and occurs in less than 1% of adults with acute hepatitis B. Case fatality of fulminant hepatitis is 20-33% unless liver transplantation can be performed.[3] In the past 10 years Statistics Netherlands (CBS) reported 18 deaths from acute hepatitis B. However, the disease burden from HBV infection is

mainly related to cirrhosis and hepatocellular carcinoma as a result of chronic hepatitis B. Mortality due to chronic hepatitis B in The Netherlands was estimated at around 200 persons per year in the period 2002-2015.[4] As the majority of the burden of chronic hepatitis B is found in first generation migrants born in countries with intermediate to high prevalence of chronic HBV infection the Health Council recommended screening of these groups.[5]

3.5.4   *Assessment of the vaccination against the six criteria, issues identified*
Criterion 1. Is the protection adequate for all those intended to be protected?
In general, the current routine hepatitis B vaccination schedule offers adequate protection to all children, including preterm infants, as hepatitis B vaccines are highly immunogenic. Additional hepatitis B vaccination programmes are implemented to prevent HBV infection in children at risk of perinatal transmission and in groups at risk of sexual transmission. All pregnant women in The Netherlands are offered screened for HBsAg to detect HBV infection, with high adherance, and the coverage of immunoglobuline and a birth dose of hepatitis B vaccine in children of mothers with HBV infection is high too. The hepatitis B vaccination programme for MSM and sexworkers remained in place after introduction of general hepatitis B vaccine of infants in the NIP.

Issue related to criterion 1
  i.   Hepatitis B vaccination for groups at higher risk of infection needs continuous attention and monitoring.

Criterion 2. Is the applied vaccination strategy optimal?
Yes, most of the population is sufficiently protected. The uptake of hepatitis B vaccination is high, with 93% for the cohort born in 2018.[6]

No issue related to criterion 2

Criterion 3. Does the programme include too much?
Maybe. A full vaccination series should consist of two priming doses followed by a third dose. The NIP schedule used for most infants consists of three doses, but children of mothers with chronic HBV infection and children from mothers who did not get pertussis vaccination in pregnancy receive two and one more doses, respectively, than deemed sufficient.

Issue related to criterion 3
  ii.   Can the number of hepatitis B vaccine doses be reduced for children of mothers with HBV infection and children from mothers who did not get pertussis vaccination in pregnancy?

Criterion 4. Does the programme include too little?
No. Additional doses are not needed after a complete 3-dose vaccination series. In studies up to 30 years after introduction of vaccination effective protection was shown.[7]

Criterion 5. Is the timing of immunisations using combination vaccines optimal or at least acceptable?
Yes. The routine schedule for children from HBsAg negative mothers starts at three months of age. The current schedule includes a minimum interval of at least one month between doses. World wide, the first two priming doses are historically given one month apart. In order to reach effective immunity as soon as possible in children from mothers with chronic HBV infection, after a birth dose these children receive the second dose at two months of age. Would it be acceptable for children of mothers with chronic infection to receive their second dose at three months as part of the regular NIP schedule?

Issue related to criterion 5
iii. Can the interval between the birth dose and the second dose of hepatitis B vaccine be increased to three months for children of mothers with chronic HBV infection?

Criterion 6. Are there important drawbacks of the NIP? For the population as a whole? For those who opt out? How are these drawbacks to be weighed against the advantages of the programme and its components?
No drawbacks are known.

3.5.5 *Exploration of the issues against available evidence*
Hepatitis B vaccination for groups at higher risk of infection needs continuous attention and monitoring
An important risk group for HBV infection are children from mothers with HBV-infection. A birth dose is needed to prevent perinatal transmission of HBV. As the NIP does not include a birth dose for all infants, additional measures are currently taken to protect children at risk of perinatal transmission. The antenatal screening programme identifies pregnant women with chronic HBV infection. Infants born to mothers with chronic HBV infection are given hepatitis B immunoglobulin (HBIG) within 2 hours of birth and an additional vaccination against hepatitis B (birth dose) within 48 hours. These infants receive an extra dose of vaccine at 2 months followed by the doses of the regular vaccination schedule at 3, 5 and 11 months, all of these as part of the DtaP-IPVHepBHib combination vaccine. A deliberate choice was made to follow the routine schedule where possible as deviations therefrom are prone to error.

Evaluation of the antenatal screening and immunisation programme shows that the prevalence of chronic HBV infection among pregnant women is relatively constant at about 0,3% and yearly about 500 children are born whose mothers are infected with HBV. A small decline in HBsAg prevalence is observed, it was 0,26% in 2019 (n=437 children) The evaluation also shows the coverage of the antenatal screening is very high with >99%, and for children of mothers with HBV infection the birth dose coverage is 99% and the coverage of HBIG at birth was 99.8% with 73-80% administered within 2 hours.[8] Complete vaccination measured as having received HepB4 at age 2 years was 98%.[6]

Although rare, even after giving HBIG and vaccination at birth, HBV infection among children born to chronically infected mothers can still occur. Serological evaluation by the RIVM of these children after completion of the vaccination series over the period 2006-2011 showed that a breakthrough infection occurred in 0.5% (17/3199).[9, 10] The risk of breakthrough infections is greatest in children of mothers who are hepatitis B e-antigen (HBeAg) positive which is a proxy for a high viral load. In this group breakthrough infections occurred in 5,2% (15/288). Antiviral treatment of pregnant women with a high viral load in the third trimester reduces the risk of a breakthrough infection.[11] Referral and treatment of pregnant women is included in antenatal care guidelines in The Netherlands and received more attention since 2008.[12] Recent information on treatment of pregnant women is not available but it is known that in the past three years (2017-2019), 91-94% of HBeAg-positive women were referred to specialist care.[8]

Table 1 Breakthrough infections in children born in The Netherlands from mothers with chronic HBV infection by period and vaccination schedule.

Period	HBIg month (dose)	Vaccine month (type)	N HBeAg+	HBsAg+ infants from HBsAg and HBeAg+ mothers	HBsAg+ infants from all HBsAg+ mothers
1982-1984*	0 (200)	0, 1,2,11 (p10)	42	3 (7,1%)	
1982-1984	0,3 (200,125)	3,4,5, 11 (p10)	41	3 (7,3%)	
1988-1989	0 (300)	3,4,5, 11 (r20)	14	1 (7,1%)	
1988-1989	0,3 (300,300)	3,4,5, 11 (r20)	17	1 (5,9%)	
1982-1989			114	8 (7,0%)	
2003-2005	0 (300)	2,4,11			8/1225 (0.7%)
2005-2006	0 (300)	0,2,4,11			1/150 (0.7%)
2003-2007	0 (300)	0,1,6 (A'dam)			1/335 (0,3%)
2006-2011	0 (300, 150)^	0,2,3,4,11			7/1489 (0.5%)
2003-2011			288[#]	15 (5,2%)	17/3199 (0,53%)
2003-2011	Excl. A'dam				16/2864 (0,56%)

In 2012 the serological evaluation became the responsibility of youth health care and the general practitioner but an evaluation in 2014 indicated the result of serological evaluation was only available for half of the children. In the period 2012 to 2020 only two children with breakthough infections were reported, i.e. children who were born in The Netherlands since 2003 and had been vaccinated but were diagnosed with a chronic HBV infection. The low number of reported breakthrough infections can be related to antiviral treatment of pregnant women but with suboptimal serological evaluation breakthrough infections could also have been missed.

The monitoring and evaluation data indicate the antenatal screening and vaccination programme to prevent perinatal transmission are effective.

The other risk group for which additional hepatitis B vaccination is implemented outside the NIP are MSM and sex workers. As hepatitis B vaccination for all infants is included in the NIP since 2011, it will take many years before the programme for sexual risk groups becomes obsolete. A modeling study suggested that universal vaccination may result in a reduction of 24% of the total number of HBV infections among MSM estimated to occur from 2020 to 2070. Compared to continuing until 2070, quitting risk-group vaccination in 2030 or 2040 may result in 30% or 10% more HBV infections over 2020-2070, respectively,. With PrEP and risk-group vaccination the total number of HBV infections over 2020-2070 may be reduced by 13%.[13]

Can the number of hepatitis B vaccine doses be reduced for children of mothers who test positive for HBsAg during antenatal screening and children from mothers who did not get pertussis vaccination in pregnancy? Can the interval between the birth dose and the second dose of hepatitis B vaccine be increased to three months for children of mothers with chronic HBV infection?
The WHO recommends a 3 or 4 dose vaccination schedule for infants with a minimum interval between doses of 4 weeks. The producers of the combination vaccines used in the NIP recommend an interval of at least 6 months before the last dose. Historically, the standard three-dose schedule consists of two priming doses given 1 months apart, and a third dose 6 months after the first. A longer interval between the first and second dose has little effect on immunogenicity.[3] Longer intervals between the last two doses result in higher final antibody concentrations but not higher seroconversion rates.[3] Multiple schedules are in use as it is recommended to add hepatitis B vaccine to existing programmes without requiring additional visits. A frequently used schedule is that with vaccinations at 0, 1 and 6 months. An international meta-analysis of 29 trials found no significant difference in the incidence of HBV infection between different schedules, differences in dosage and vaccine type.[14] This is also the case for data from The Netherlands (Table 1). To achieve protection against hepatitis B a schedule with 3 doses would be sufficient.

Regarding the timing of the doses, children from mothers with HBV infection need to receive the first dose at birth. To answer the question if the interval between the birth dose and the second dose can be increased to 3 months, Dutch data from the 1980s that did have an interval of 3 months are limited and difficult to compare as they partly included an extra dose of HBIG at 3 months (Table 1). Also none of the studies in the metanalysis had a schedule with a birth dose and the 2nd dose at 3 months. The WHO therefore states that there is insufficient data to determine whether an interval of more than 2 months between the 1st dose at birth and the 2nd dose does result in a lower effectiveness of vaccination. Countries in Europe with NIP schedules with the 1st vaccination at 3 months generally have an adjusted schedule for children of mothers with HBV infection. In Italy, Denmark and Sweden these children receive a birth dose and the second dose at the age of 1 month, from the 3rd vaccination the routine schedule is followed.

The group of children of mothers with a chronic HBV infection are exposed to HBV during childbirth and are at much increased risk of becoming chronically infected themselves. There is insufficient evidence to substantiate whether delaying the 2nd dose of hepatitis B vaccine from 2 to 3 months of age has a negative effect on the occurrence of breakthrough infections. Thus, from the precautionary principle, it is recommended to give this group of children the 2nd dose of hepatitis B vaccine earlier than at the age of 3 months, i.e. at 4 to 8 weeks. Children from mothers with chronic HBV infection receive more doses of hepatitis B vaccine, specifically a birth dose and the second dose at two months of age. The second dose could be given as a stand alone hepatitis B vaccine for children who do not need additonal pertussis vaccination. After the second dose these children can continue to follow the routine schedule, vaccinations at 3, 5, and 11/12 months.

3.5.6 *Summary and conclusions; suggestions for the request for advice from the Health Council*
A routine vaccination schedule for primary prevention of hepatitis B includes three doses. The interval between doses is a minimal four weeks but this can be longer. The schedule is therefore flexible and in the routine schedule the first dose can be given between 6 weeks and 3 months of age, the second dose at least four weeks later and the last dose after an interval of at least six months. The currently used schedule with doses at 3, 5, and 11 months meets these requirements.

Children of mothers with chronic HBV infection constitute a special group. These children need secondary prevention in order to avoid becoming chronically infected. The ideal vaccination schedule for this group of children, as recommended by WHO, should include doses at birth, one and six months of age. In the Dutch NIP these children receive two early doses of hepatitis B vaccine, at birth (*stand alone*) and at two months of age (as DtaP-IPVHepBHib combination vaccine). For children who do not need additional protection against pertussis, the second dose could also be replaced by a hepatitis B *stand alone* vaccine. From thereon the immunization schedule for children of mothers with chronic HBV infection currently follows the routine schedule with doses at 3, 5 and 11 months of age (as combination vaccine).

It should be noted that children of mothers with chronic HBV infection receive more doses of hepatitis B vaccine than necessary. Since there is a lack of evidence to assess whether delaying the two month-dose to three months of age – thus avoiding an extra dose – would have no negative effect on protection, the extra dose at two month of age should be maintained until further data become available.

3.5.7 *References*
1. Sonneveld, M.J., et al., *Decrease in viral hepatitis diagnoses during the COVID-19 pandemic in the Netherlands.* J Hepatol, 2021.
2. Koopsen, J., et al., *Chronic hepatitis B and C infections in the Netherlands: estimated prevalence in risk groups and the general population.* Epidemiol Infect, 2019. **147**: p. e147.
3. Van Damme, P., et al., *Hepatitis B Vaccines*, in *Plotkin's Vaccines*. 2018, Elsevier: Philadelphia, PA.
4. Hofman, R., et al., *[Mortality due to chronic viral hepatitis B and C infections in the Netherlands].* Ned Tijdschr Geneeskd, 2016. **160**(0): p. D511.
5. Gezondheidsraad - Health Council of the Netherlands, *Screening risk groups for hepatitis B and C [in Dutch]*. 2016: Den Haag.
6. van Lier, E.A., et al., *Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2020*. 2021, RIVM: Bilthoven.
7. Pattyn, J., et al., *Hepatitis B Vaccines.* J Infect Dis, 2021. **224**(Supplement_4): p. S343-S351.
8. van der Ploeg, C.P.B., P. Oomen, and M. van Lent, *Prenatale Screening Infectieziekten en Erytrocytenimmunisatie (PSIE) Procesmonitor 2019*. 2021, RIVM/TNO.
9. Hahne, S., et al., *Prevention of perinatal hepatitis B virus transmission in the Netherlands, 2003-2007: children of Chinese mothers are at increased risk of breakthrough infection.* Vaccine, 2012. **30**(9): p. 1715-20.

10. van Heiningen, F.M., et al., *Effectevaluatie Preventie Perinatale HBV-transmissie*. 2012, RIVM: Bilthoven.
11. Pan, C.Q., et al., *Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load.* N Engl J Med, 2016. **374**(24): p. 2324-34.
12. van Heiningen, F.M. and S.J.M. Hahne, *Antivirale therapie voor zwangere vrouwen met chronische hepatitis B.* Infectieziekten Bulletin, 2014. **25**(3): p. 80-81.
13. Xiridou, M., et al., *Ending risk-group HBV vaccination for MSM after the introduction of universal infant HBV vaccination: A mathematical modelling study.* Vaccine, 2021. **39**(21): p. 2867-2875.
14. Lee, C., et al., *Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis.* BMJ, 2006. **332**(7537): p. 328-36.

3.6 Invasive disease by Haemophilus influenzae type b

3.6.1 History of vaccination against invasive disease by Haemophilus influenzae type b

Vaccination against invasive disease by *Haemophilus influenzae* type b (Hib) was introduced in the NIP of The Netherlands in April 1993 as a separate vaccine that was administered simultaneously with the tetravalent vaccine against diphtheria, pertussis, tetanus and polio. The vaccine was administrated according to a 3+1 schedule, with three primary doses at 3, 4 and 5 months and one booster dose at 11 months. Since then, several changes in the Hib vaccination schedule have occurred (Figure 1)[1].
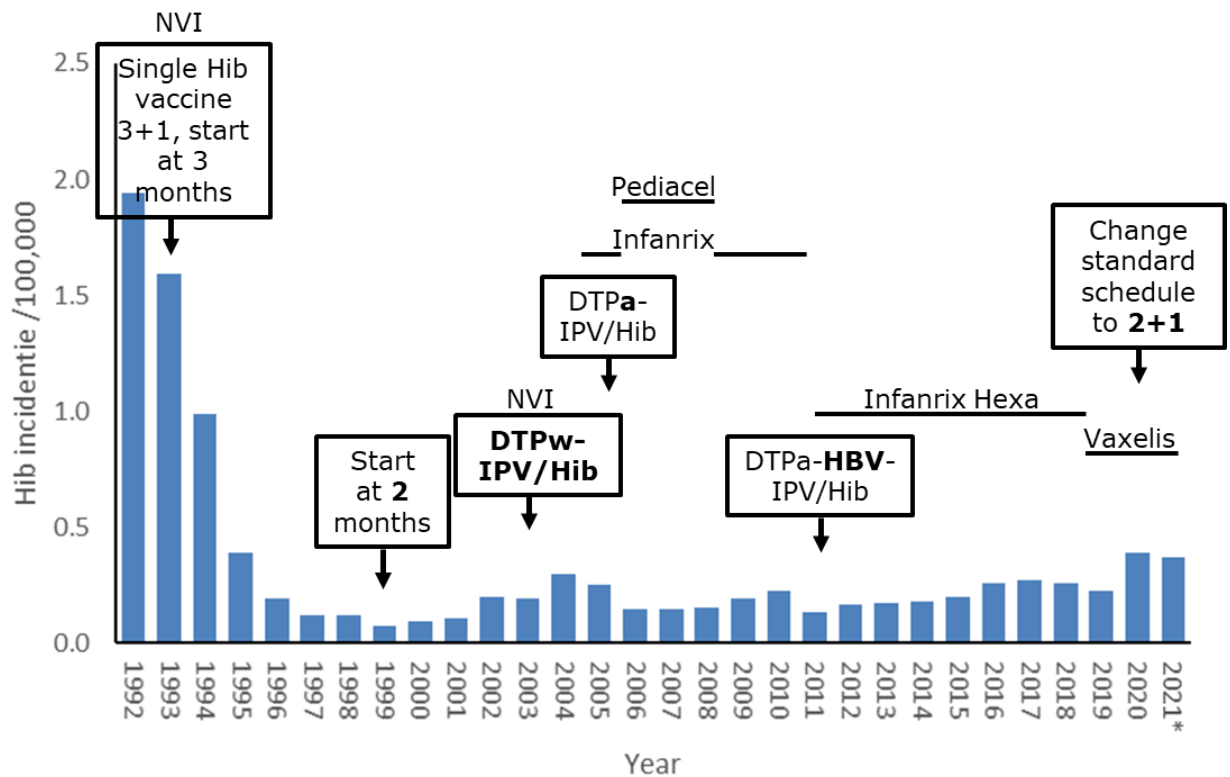
Figure 1 Incidence of invasive disease by Haemophilus influenzae type b for the Dutch population and the changes in the National Immunisation Programme that are relevant for Hib (indicated in bold). NVI=Netherlands Vaccine Institute; DTP=diphtheria, tetanus pertussis whole cell (Pw) or acellular (Pa); IPV=inactivated poliovirus vaccine; HBV=hepatitis b vaccine; Hib=Haemophilus influenzae b; 3+1= 3 primary doses and 1 booster dose; 2+1= 2 primary doses and 1 booster dose.

From 2003, Hib vaccine is administered as part of a combination vaccine. First in pentavalent vaccines containing whole cell pertussis (DTwP-IPV-Hib) up to 2005, and subsequently with an acellular pertussis components vaccine (DTaP-IPV-Hib) up to 2011. In August 2011, hepatitis B (HBV) vaccination was added to the programme through the change to a hexavalent vaccine. From 2019, the hexavalent product has been changed from DTP3a-HBV-IPV/Hib (Infanrix hexa; up to cohort 2018) to DTP5a-HBV-IPV/Hib (Vaxelis; cohort 2019 onwards). These hexavalent vaccines mostly contain similar vaccine antigens, including the most important virulence factor for Hib: the capsular polysaccharide polyribosylribotol phosphate (PRP). However, in addition to two extra pertussis antigens (Fim2 and Fim3), DTP5a-HBV-IPV/Hib and DTP3a-HBV-IPV/Hib differ in the composition of the carrier compound, adjuvant and PRP length which results in a different immunological response [2]. The most recent change in the NIP for Hib was implemented in 2020; the schedule changed from 3+1 to 2+1 because of the introduction of maternal pertussis vaccination. An exception is made for some specific groups, including prematurely born children and children born from mothers that were not vaccinated at least 14 days before delivery; these children obtain a 3+1 schedule at 2, 3, 5 and 11 months.

3.6.2   *Goal of vaccination against Haemophilus influenzae type b*
The main purpose of vaccination against invasive disease caused by
Haemophilus influenzae type b (Hib-ID) is to prevent invasive disease,
including meningitis, sepsis and epiglottitis, among children under five
years of age, i.e., to protect as many individuals in the vulnerable
group(s) as possible. A second aim is to indirectly protect the rest of the
population. These goals can be achieved by a combination of individual
protection of children and aiming for as much reduction in circulation as
possible in The Netherlands; because of its biology, herd immunity will
likely not be reached for Hib even at high vaccine coverage [3].

3.6.3   *Epidemiology of invasive Hib disease in The Netherlands*
Before introduction of vaccination, each year over 100 cases of Hib-ID
occurred in children younger than 1 year of age. Among children
younger than five, more than 250 Hib-ID cases occurred yearly (1992:
278). Few cases were observed above that age. The overall incidence
was 1.9/100,000, with the highest incidence among children younger
than five years (28.9/100,000). Note that invasive Hib disease (almost)
always necessitates hospitalization.

After vaccine introduction, Hib-ID has become an uncommon disease in
The Netherlands with a yearly incidence of less than 0.4/100,000 in the
last decade, i.e., around 40 cases per year. Despite vaccination, the
incidence is still highest in those under five year of age (about 40% of
the cases), followed by those aged 65+ (about 25-35% of the cases -
Figure 2). However, the incidence is increasing among children younger
than 5 years since 2012 from <1/100,000 to 3.3/100,000 in 2020 and
2.6/100,000 in 2021 up to and including September. An increase has
also been observed in other age groups in 2020-2021 (Figure 2). In the
period 1996-2019, an average incidence of 0.2/100,000 in the overall
population was seen. In 2020 and 2021, the incidence was
0.39/100,000 and 0.33/100,000, respectively. This increase occurred
despite the presence of preventive measures against COVID-19
including social distancing and school closures during part of 2020-2021.
The incidence of other, non-b, *Haemophilus influenzae* types decreased
during the pandemic period (Figure 3). It is currently being investigated
whether the increase is related to recent changes in the NIP or whether
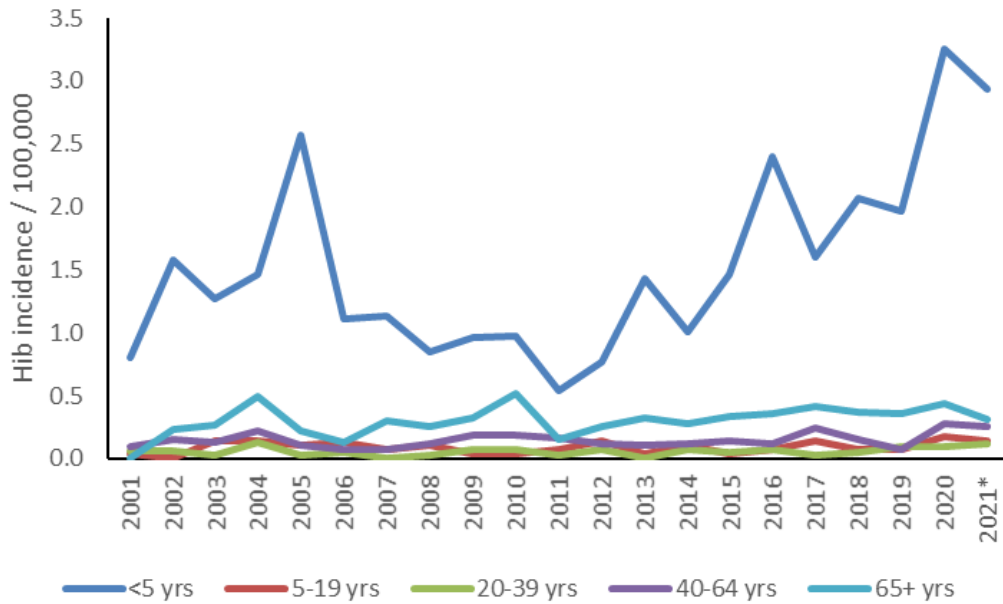other reasons may explain the increased incidence [4].

Figure 2 Age-specific Hib incidence for the period 2001-2021.Data for 2021 are extrapolated from data up to and including September 2021.
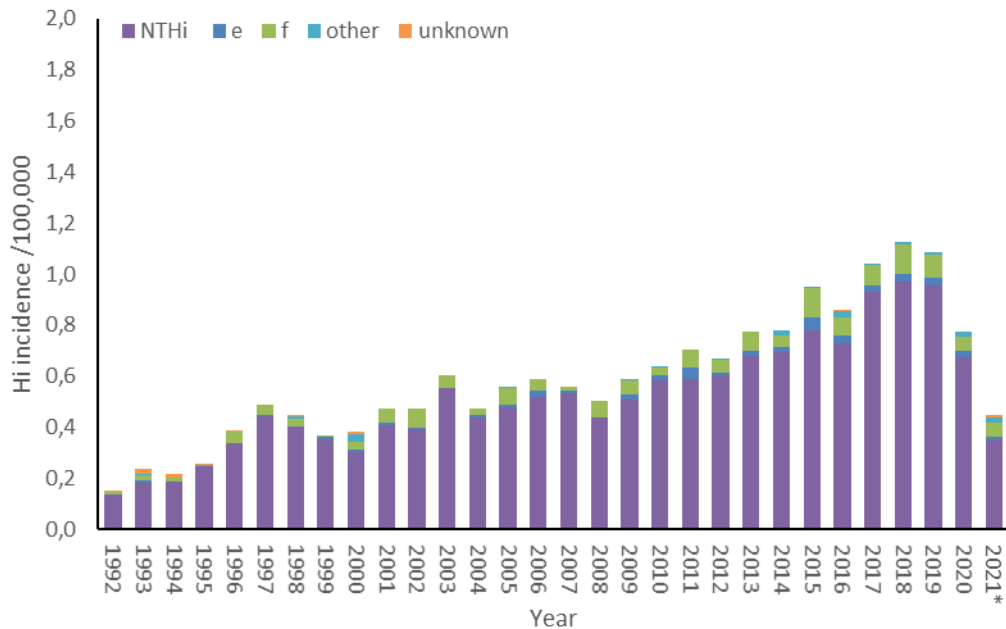

Figure 3 Incidence of invasive disease caused by non-b type Haemophilus influenzae (Hi). Data for 2021 are extrapolated from data up to and including August. NTHi = non-typeable Haemophilus influenzae.

3.6.4   *Assessment of the vaccination against the six criteria, issues identified*
Criterion 1. Is the protection adequate for all those intended to be protected?
Partly. Before the introduction of vaccination, the highest burden of Hib-ID was found among children under 24 months of age, and specifically those younger than one year [5]. Since the introduction of vaccination, the incidence of Hib-ID has decreased rapidly. Although the

effectiveness of Hib-containing vaccines is good, still 15-20 cases occur among infants and toddlers yearly (on average in 2015-2021: <1 yrs: n=7, 1-2 yrs: n=8, 3-4 yrs: n=4). About half of the cases <5 years old are fully vaccinated against Hib. Generally, the incidence of Hib-ID is higher in The Netherlands compared to most other European countries, although this may also be caused by differences in surveillance practice [6, 7]. Recently, the incidence has increased further. The number of infant and toddler cases as well as the increase in Hib-ID incidence show that protection is not optimal with the current vaccines/vaccination schedule.

There seem not to be specific problems with the protection of specific groups such as prematurely born children or immunocompromised children [8]. However, immune responses are generally lower in prematurely born children, also for Hib, and the lower immune response remains after the booster dose [9, 10].

Issues related to criterion 1
I: There are still Hib cases in the targeted age group and indirect protection seems incomplete.
II: In the last few years an increase in the incidence of Hib-ID cases was observed. The cause should be further investigated.

Criterion 2. Is the applied vaccination strategy optimal?
Although Hib vaccination is effective and provides at least partial herd protection, such protection is not complete. Individual protection remains the most important strategy.

The immune response to vaccination with Hib-PRP is limited in children in the first year of life, and a booster vaccination is therefore required for sufficient, long lasting protection. The booster at 11 months comes quite early, compared to many other European countries [11]. A booster provided at a slightly later age may induce a better immune response. Additionally, reduction of nasopharyngeal carriage by vaccination and thereby prevention of circulation in the population, may improve if the booster would be provided at a slightly higher age. Such decrease is expected based on the fact that immunity may last longer and carriage rates are (before vaccine introduction) highest at three to five years of age [12], even though also at that age, Hib carriage is limited [13, 14].

Issues related to criterion 2
Is the booster given too early?

Criterion 3. Does the programme include too much?
No, the programme does not include too much, as there are still infant and toddler Hib cases and the incidence increases. In addition, the schedule was recently changed from 3+1 to 2+1, which needs to be closely monitored in the coming years (see next paragraph).

Issues related to criterion 3
none.

Criterion 4. Does the programme include too little?
Too early to say. In 2020, the schedule was reduced from 3+1 to 2+1 doses. A recent French seroprevalence study suggested that a 3+1 schedule provides likely a more robust immune response than the 2+1 schedule [15]. It is not yet known whether this reduction in number of primary vaccinations plays a role in the higher number of cases that have been observed in 2020-2021; further investigations are ongoing.

Issues related to criterion 4
Recently, the vaccination schedule was reduced from four to three doses (2020). This change should be evaluated for effectiveness.

Criterion 5. Is the timing of immunisations using combination vaccines optimal or at least acceptable?
Compared to many other European countries [11], the booster is given quite early in The Netherlands. Delaying the booster dose may provide better direct and indirect protection based on immunological data [16]. There may occur some additional cases occurring in the months before the booster is provided but is it expected that that number will be outweighted by fewer cases after the booster including better herd immunity.

Issues related to criterion 5
Is the booster given too early?

Criterion 6. Are there important drawbacks of the NIP? For the population as a whole? For those who opt out? How are these drawbacks to be weighed against the advantages of the programme and its components?
There are no clear drawbacks of vaccination against Hib; not for the overall population, nor for those refusing vaccination. Up to now there has not been clear evidence for replacement [17], as generally seen after the introduction of pneumococcal conjugate vaccines. Still, it should be noted that in The Netherlands, the incidence of invasive disease caused by non-typeable *Haemophilus influenzae* (NT-Hi) has been higher since Hib vaccination than before and has (further) increased since 2012, and a similar increase has been seen in other European countries, the UK and Ontario, Canada [6, 18-20]. Invasive disease caused by NT-Hi is mainly seen among older adults. For NT-Hi, there is currently no vaccine available.

Issues related to criterion 6
Does replacement play a role for *Haemophilus influenzae*?

Encountered issues:
   a. There are still cases in the targeted age group and indirect protection is incomplete. This shows that there is room for further improvement.
   b. The number of Hib infections among infants and toddlers is increasing. Furthermore, in 2020-2021 also the incidence of Hib-ID in non-vaccinated age groups was higher than before. It should be investigated whether recent changes in the NIP play a role in the increase.

c. The booster (at 11 month) is given early compared to other countries. Is it too early?

d. Recently, the vaccination schedule was changed from 3+1 (2, 3, 4, 11 months) to 2+1 (3, 5, 11 months). Evaluation of this change is necessary.

e. Does replacement play a role for *Haemophilus influenzae*?

3.6.5 *Exploration of the issues against the available knowledge*

Can direct and indirect protection be improved?

Direct protection against Hib can be induced through vaccination. Since the introduction of vaccination against Hib in 1993, vaccine coverage has been high. The vaccination coverage for Hib at 2 years of age was highest for cohorts 2008-2009 at 96.0% (in 2010-2011) and has been around 93-94% since cohort 2014. The most recent data show a coverage for the primary series of 94.2% and for completing the schedule 93.8% (cohort 2018 [21]). Among the cases that were eligible for vaccination, i.e., are born in or after April 1993, on average 62% had received the number of doses as recommended in the schedule and was therefore assumed to be sufficiently vaccinated in the period from 2003-2021 (Figure 4). Using the screening method, the vaccine effectiveness has been estimated to be quite stable over time and above 90% (Figure 4). Vaccine effectiveness estimates were confirmed by a case-control study including data of 2003-2016 that found an overall VE of 93% (89-95) with no change over time and no difference between the pentavalent vaccine (92%, 95%CI 86-95) and the hexavalent vaccine (94%, 95%CI 89-97%) [22]. The VE was found to decrease with age of diagnosis, with 97-99% at 1-2 years and 61-82% at 3-4 years. We have planned a new study to estimate the product- and schedule-specific vaccine effectiveness at different time since vaccination during recent years.
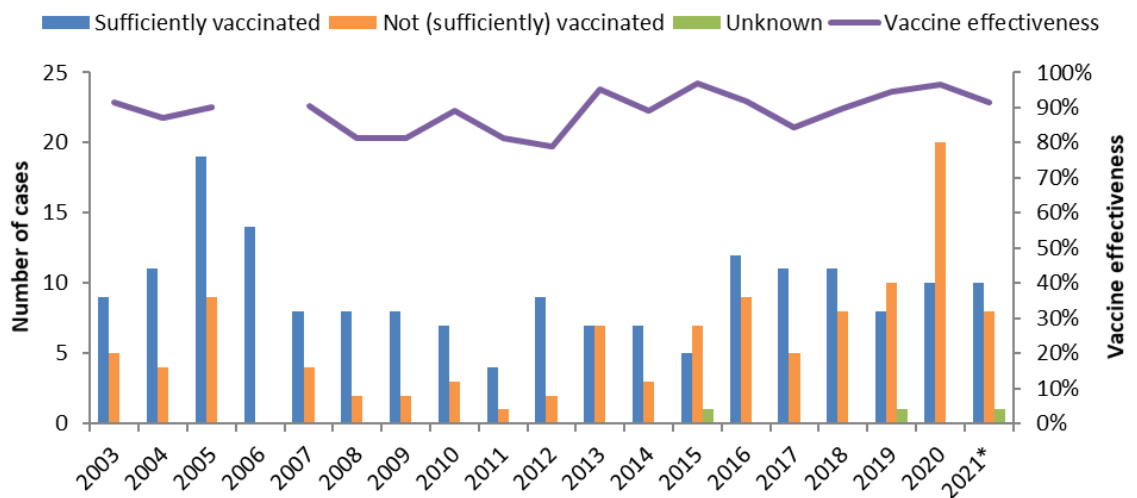

Figure 4 The number of cases eligible for vaccination (older than 3 months and born in or after April 1993 by vaccine status, and the estimated vaccine effectiveness. Data for 2021 are up to and including September.

On average, roughly 10 vaccine failures occur annually, of which the youngest of these vaccinated cases were 7 months of age (in the years

2012-2021; Figure 5). Although the numbers are very small, we see a small increase in the number of vaccine failures by age in the months after receiving the primary series (2 cases at 7 month of age, 5 cases at 10 months of age). Generally, the booster is given at 11-12 months. No cases were observed in the first year after the booster (up to the age of 21 months).
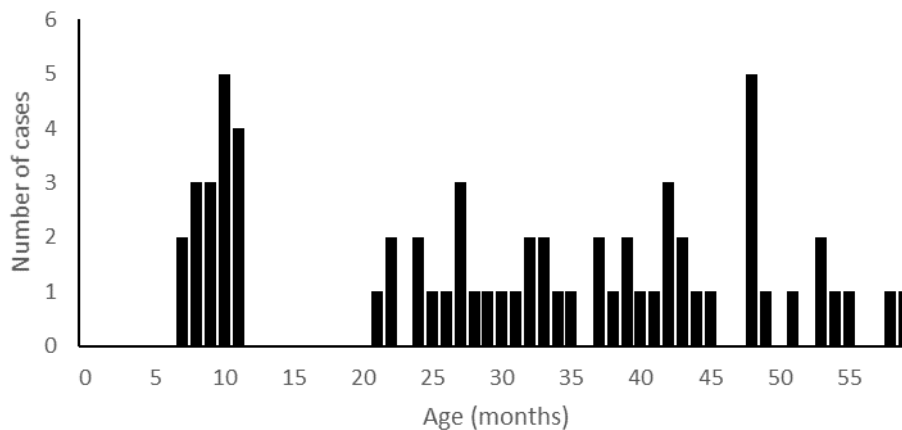

Figure 5 Histogram of Hib cases in sufficiently vaccinated children aged younger than 5 years in the years 2012-2021 (up to and including September 2021) by age in months. Being sufficiently vaccinated is defined for those <12 months as having received ≥2 doses of Hib-containing vaccine. For those aged ≥1 year, having received the primary series and a booster at 11 months or ≥1 dose given after the first birthday would count as being sufficiently vaccinated. Doses only counted if obtained >14 days before disease onset.

Indirect protection occurs through herd effects of vaccinated individuals by reducing carriage and thereby transmission. The incidence of Hib in those not targeted for vaccination (aged 5 years and older) seemed to decrease after vaccine introduction in 1993, however, from 2002, the incidence in those 5 years and older has fluctuated between 0.1-0.2/100,000 (Figure 6). As shown above, in 2020 and 2021, the incidence was slightly higher (0.24/100,000 and 0.21/100,000, respectively), and this included an increase in non-vaccinated age groups. The extent of indirect protection is difficult to estimate based on the incidence figures as it is, of course, not known how the incidence would have developed over time without vaccination. Still, indirect protection seems limited in The Netherlands, and possibly more limited than described for other countries [18]. As seen in other countries where Hib is present in the NIP [13, 14], carriage of Hib isolates is very low; based on preliminary analysis of data from a Dutch carriage study performed in 2018 among 2-years-olds and their parents, 0 out of 330 children that carried *Haemophilus influenzae* carried serogroup b and 3 out of 330 parents carried Hib (personal communication Rob Mariman, 01-11-2021). To prevent Hib carriage, higher antibody levels are needed compared to prevention of clinical disease [23].
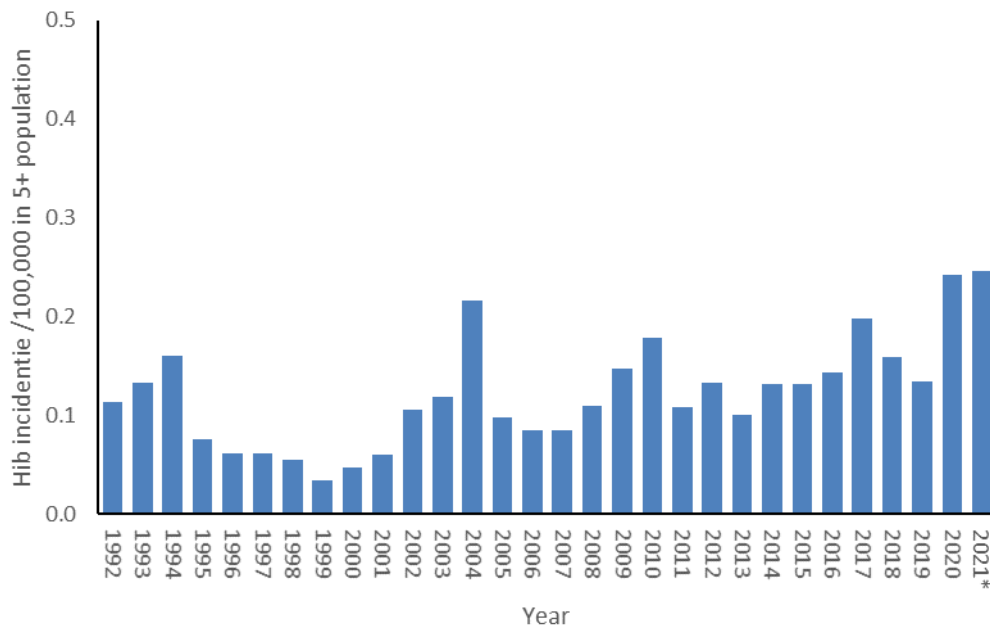
Figure 6 The incidence in the population aged 5 years and older. Data for 2021 are extrapolated from data up to and including August.

What may be the reasons for the recent increase in Hib cases?
As shown in Figure 2, the incidence in the under-fives has been increasing since 2012 and the incidence in the non-vaccinated age groups was also higher in 2020-2021. There may be several reasons that play a role in the increase in Hib cases, including methodological, behavioural, vaccine-related or biological factors, including the amount of immunity and thus conversely, the proportion of susceptible persons present in the population as well the prevalence of specific Hib clones and their invasive capacity [4].

The Dutch cross-sectional Pienter 1 and Pienter 2 serological surveys were conducted in 1995/1996 and 2006/2007, respectively. The concentrations of Hib IgG in serum from children up to the age of 11 months were higher in Pienter 1 than in Pienter 2 [24]. After the booster age, the difference was no longer present. The cause of this difference post-primary vaccination is unknown, but maybe related to the change in vaccine and schedule as well as reduced natural boosting in the general population due to reduced circulation. This last possibility was suggested by the finding that the IgG concentrations in the first few months prior to vaccination were reduced in Pienter 2. In these first months of life, the detected antibodies are maternal antibodies transferred placentally [25]. In the third Pienter study (2016/2017) it is notable that persons aged 6-20 years show slightly higher concentrations of Hib-specific antibodies compared to children aged 2-6 years [26]. The higher concentrations in children aged >6 years compared to younger children may be explained by the switch from the pentavalent to the hexavalent vaccine in 2011, as the older cohorts therefore received a different vaccine than younger cohorts (Figure 1). The antibody level is important for the extent of direct and indirect protection as clinical disease can already be prevented at lower antibody

levels while protection against carriage requires higher antibody levels [23].

Whether or not the product change in 2019 or the schedule change in 2020 may play a role in the recent increase is unknown. Immunological data shows that the immune response to DTP5a-HBV-IPV/Hib is slightly different from the one to DTP3a-HBV-IPV/Hib. After the primary series, DTP5a-HBV-IPV/Hib leads to higher IgG concentrations, while after the booster response DTP3a-HBV-IPV/Hib leads to higher IgG concentrations [27]. In addition to antibody concentrations, avidity is an important measure for the functionality of antibodies. It is therefore interesting to note that the avidity of IgG antibodies induced by a PRP vaccine conjugated to tetanus toxoid was higher than IgG antibodies induced by a Neisseria outer membrane complex conjugated PRP vaccine [28]. In DTP5a-HBV-IPV/Hib, PRP is conjugated to outer membrane protein complex (OMPC) of *Neisseria meningitidis* and adsorbed on amorphous aluminium hydroxyphosphate sulfate (AAHS) [29]. In DTP3a-HBV-IPV/Hib, PRP is conjugated to tetanus toxoid as carrier protein and adsorbed on aluminium phosphate (AlPO4) [30].

Is the booster given too early?
The booster dose is important as clinical protection against Hib-ID wanes over time after primary vaccination [31, 32]. Furthermore, the booster dose can reduce carriage and thereby induce indirect protection [33-36]. In The Netherlands, indirect protection seems quite limited (Figure 4). It has been shown that a booster given at the age above 1 year old induces stronger antibody responses compared to a booster given at 6-11 months [37]. In different modelling studies it was suggested that delaying the booster dose within the average duration of protection of the primary doses may be beneficial to further reduce carriage and to reduce the reproduction number and thereby to reduce the number of cases [36, 38]. A meta-analysis of 2013 that compared immunological data of clinical trials did not find differences between a longer versus a shorter interval between primary and booster doses [39].
Several other (European) countries provide the booster at a slightly later age compared to The Netherlands [11]. E.g., the Scandinavian countries as well as UK [18] give the booster at 12 months, Belgium, Greece and Croatia give the booster at 15 months and Hungary, Lithuania, Malta and Portugal give the booster at 18 months. Although data are available on the Hib incidence in the different European countries [7], the large difference in Hib incidence may indicate that not all countries perform serotyping on Hi isolates of all cases and that the reported incidences are likely an underestimation of the true incidence. These data should therefore be interpreted with caution. Still, since no other data are available, the notification rate of Hib-ID in The Netherlands is quite high compared to other European countries, as is the incidence in the Scandinavian countries. The Scandinavian countries give a 2+1 schedule with their booster at 12 months. The UK uses a 3+1 schedule with the booster provided at 12 months. UK has a lower Hib incidence than the Scandinavian countries [18]. Whether the different product in the UK (Hib/MenC), the extra primary dose or other reasons explain the difference is unknown. The timing of the booster is likely better at 12 or possibly 15 months, compared to 11 months. Because of the, generally,

largest burden of Hib in children aged 4-18 months [40], direct protection of toddlers is important and the booster should therefore not be given too late. However, it should be determined whether or not a delay from 11 months to 12 months would improve herd protection; modelling studies do suggest such an effect [36, 38]. The UK concluded based on a seroprevalence study that 89% of children had anti-PRP concentrations above the threshold for short-term protection against Hib-ID, but antibodies wane quickly after the 12-months booster and antibody levels may therefore not be high enough to prevent carriage among toddlers [18].

In an open label randomised parallel controlled trial performed in The Netherlands in 2014-2016, infants were vaccinated with DTP3a-HBV-IPV/Hib at 3, 5 and 11 months [41]. The study showed that only after the booster dose, all children showed antibody concentrations above the presumed protective cut-off of 0.15 µg/mL. In this study, 71% and 83% of the children had IgG concentrations >0.15µg/mL at the age of 6 and 11 months (pre-booster), respectively. In children receiving a booster vaccination at 12 or 15 months, antibody levels of 8.2 and 14.7 ug /mL were observed at 13 and 16 months of age, respectively [42]. It needs to be noted that in these groups also different priming schedules were used that showed higher antibody concentrations in the 15 months booster groups after priming already. However, also other studies indicate that delayed boosting results in higher concentrations of Hib-specific antibodies, as well as later age of primary immunisation, the latter probably due to the presence of maternal antibodies [16]. Delayed primary immunisation may also induce higher concentrations of antibodies [16]. The implications of slightly reduced concentrations on the functionality of the antibodies and protection against disease is, however, still topic of debate [43].

The effectiveness of a reduced schedule (from 3+1 to 2+1) should be evaluated
Hib vaccination started in 1993 at 3, 4, 5 and 11 months of age. In the period 1999 - 2019, the schedule changed for all children born from 1999 onwards to 2, 3, 4 and 11 months. Since January 2020, the Hib-combination vaccine is given at 3, 5 and 11 months except for prematurely born children and children born from mothers that did not get maternal pertussis vaccination (combination vaccine against diphtheria, pertussis, tetanus); for them, vaccination is given at 2, 3, 5 and 11 months. If vaccination has started after the age of 12 months, only 1 vaccination is needed to be fully vaccinated. An evaluation of the change from the 3+1 to the 2+1 schedule is needed, but time since the change is still short and the switch occurred only one year after the change in the vaccine used and simultaneously with the start of the COVID-19 pandemic, which complicates the evaluation.

While a reduction of the number of primary doses seems to reduce the immune response [15], a higher age at the first dose is associated with higher IgG levels [16]. In France, the schedule was changed from 3+1 to 2+1 in 2013, with vaccination at 2, 4 and 11 months with a coverage of around 95% [42]. They reported an increase of (vaccine failure) cases in 2017-2019, all of which had received the 2+1 schedule. Furthermore, their seroprevalence data indicate a lower immune

response after the 2+1 schedule compared to the 3+1 schedule. Note, however, that the schedule in France starts at younger age (2 months) than in The Netherlands (3 months). Two trials included in a meta-analysis comparing schedules did not find differences between a 3+1 and 2+1 schedule [39].

Does serotype replacement play a role?
Haemophilus influenzae is a Gram-negative bacterium that is divided into encapsulated and non-encapsulated types (NTHi). The encapsulated types are categorized based on their polysaccharide capsule (type a-f). For type b (Hib), vaccination is available. Since the introduction of Hib vaccination the incidence of non-Hib cases, especially NTHI-cases has increased (Figure 3) and although numbers are limited, small increases in Hie and Hif are also observed (data not shown). We do not know whether there is a causal link between the introduction of Hib vaccination and the increase in NTHi disease. We cannot exclude improved surveillance leading to increased observations. The incidence of NTHi is highest among older adults.

3.6.6   *Summary and conclusions; suggestions for the request for advice from the Health Council*
Overall, the introduction of Hib vaccination into the NIP has led to a large decrease in the Hib-ID incidence in The Netherlands. However, there are still cases in the targeted age groups, both among vaccinated and unvaccinated children. Furthermore, a recent increase in Hib-ID incidence has been observed, also in targeted and the non-targeted age groups. These findings show that the vaccination schedule may not yet be optimal and should be investigated further. Furthermore, as the number of primary immunisations was reduced from a 3+1 to a 2+1 schedule, an evaluation is needed. In the Dutch NIP the booster dose comes quite early compared to other countries: postponing it to 12 or maximally 15 months may induce better direct and indirect protection. Protection of prematurely born children with the 3+1 schedule is adequate. Whether the schedule could be reduced to the standard schedule has not yet been determined.

3.6.7   *References*
1.   National Institute for Public Health and the Environment (RIVM). *De onderbouwing van het RVP en de wijzigingen (In Dutch)*. 2021; Available from: https://rijksvaccinatieprogramma.nl/3-onderbouwing-van-rvp-en-wijzigingen.
2.   Kelly, D.F., E.R. Moxon, and A.J. Pollard, *Haemophilus influenzae type b conjugate vaccines.* Immunology, 2004. **113**(2): p. 163-74.
3.   National Institute for Public Health and the Environment (RIVM), *RIVM notitie aan VWS: Een ondergrens voor de vaccinatiegraad in Nederland*. 2019.
4.   Steens, A., et al., *Increase in invasive disease caused by Haemophilus influenzae b, the Netherlands, 2020 to 2021.* Euro Surveill, 2021. **26**(42).
5.   Makela, P.H., et al., *Epidemiology of invasive Haemophilus influenzae type b disease.* J Infect Dis, 1992. **165 Suppl 1**: p. S2-6.
6.   Whittaker, R., et al., *Epidemiology of Invasive Haemophilus influenzae Disease, Europe, 2007-2014.* Emerg Infect Dis, 2017. **23**(3): p. 396-404.

7. European Centre for Disease Prevention and Control. *Surveillance Atlas of Infectious Diseases*. 2021; Available from: https://atlas.ecdc.europa.eu/public/index.aspx.
8. Monge, S., et al., *Clinical Characterization of Invasive Disease Caused by Haemophilus influenzae Serotype b in a High Vaccination Coverage Setting.* J Pediatric Infect Dis Soc, 2019. **8**(3): p. 261-264.
9. Rouers, E.D.M., et al., *Association of Routine Infant Vaccinations With Antibody Levels Among Preterm Infants.* JAMA, 2020. **324**(11): p. 1068-1077.
10. Zimmermann, P. and N. Curtis, *Factors That Influence the Immune Response to Vaccination.* Clin Microbiol Rev, 2019. **32**(2).
11. European Centre for Disease Prevention and Control. *Vaccine Scheduler*. 2021; Available from: https://vaccine-schedule.ecdc.europa.eu/.
12. Barbour, M.L., *Conjugate vaccines and the carriage of Haemophilus influenzae type b.* Emerg Infect Dis, 1996. **2**(3): p. 176-82.
13. Giufre, M., et al., *Carriage of Haemophilus influenzae in the oropharynx of young children and molecular epidemiology of the isolates after fifteen years of H. influenzae type b vaccination in Italy.* Vaccine, 2015. **33**(46): p. 6227-34.
14. Shrestha, S., et al., *Impact of Vaccination on Haemophilus influenzae Type b Carriage in Healthy Children Less Than 5 Years of Age in an Urban Population in Nepal.* J Infect Dis, 2021. **224**(Supplement_3): p. S267-S274.
15. Hong, E., et al., *Haemophilus influenzae type b (Hib) seroprevalence in France: impact of vaccination schedules.* BMC Infect Dis, 2021. **21**(1): p. 715.

16. Voysey, M., et al., *The Influence of Maternally Derived Antibody and Infant Age at Vaccination on Infant Vaccine Responses : An Individual Participant Meta-analysis.* JAMA Pediatr, 2017. **171**(7): p. 637-646.
17. Menzies, R.I., et al., *No evidence of increasing Haemophilus influenzae non-b infection in Australian Aboriginal children.* Int J Circumpolar Health, 2013. **72**.
18. Collins, S., et al., *Haemophilus influenzae type b (Hib) seroprevalence and current epidemiology in England and Wales.* J Infect, 2018. **76**(4): p. 335-341.
19. McTaggart, L.R., et al., *Increased Incidence of Invasive Haemophilus influenzae Disease Driven by Non-Type B Isolates in Ontario, Canada, 2014 to 2018.* Microbiol Spectr, 2021. **9**(2): p. e0080321.
20. Resman, F., et al., *Invasive disease caused by Haemophilus influenzae in Sweden 1997-2009; evidence of increasing incidence and clinical burden of non-type b strains.* Clin Microbiol Infect, 2011. **17**(11): p. 1638-45.
21. National Institute for Public Health and the Environment (RIVM), *Vaccinatiegraad en jaarveslag Rijksvaccinatieprogramma Nederland 2020*. 2021.
22. Monge, S., et al., *Effectiveness of the DTPa-HBV-IPV/Hib vaccine against invasive Haemophilus influenzae type b disease in the Netherlands (2003-16): a case-control study.* Lancet Infect Dis, 2018. **18**(7): p. 749-757.
23. Fernandez, J., et al., *Prevention of Haemophilus influenzae type b colonization by vaccination: correlation with serum anti-capsular IgG concentration.* J Infect Dis, 2000. **182**(5): p. 1553-6.
24. Schouls, L., et al., *Lagging Immune Response to Haemophilus influenzae Serotype b (Hib) Conjugate Vaccine after the Primary Vaccination with Hib of Infants in The Netherlands.* Vaccines (Basel), 2020. **8**(3).
25. van den Berg, J.P., et al., *Transplacental transport of IgG antibodies specific for pertussis, diphtheria, tetanus, haemophilus influenzae type b, and Neisseria meningitidis serogroup C is lower in preterm compared with term infants.* Pediatr Infect Dis J, 2010. **29**(9): p. 801-5.
26. National Institute for Public Health and the Environment (RIVM), *The National Immunisation Programme in the Netherlands. Surveillance and developments in 2020-2021*. 2021.
27. Knuf, M., et al., *Hexavalent vaccines: What can we learn from head-to-head studies?* Vaccine, 2021. **39**(41): p. 6025-6036.
28. Schlesinger, Y. and D.M. Granoff, *Avidity and bactericidal activity of antibody elicited by different Haemophilus influenzae type b conjugate vaccines. The Vaccine Study Group.* JAMA, 1992. **267**(11): p. 1489-94.
29. European Medicines Agency. *Summary of product characteristics - Vaxelis*. Available from: https://www.ema.europa.eu/en/documents/product-information/vaxelis-epar-product-information_en.pdf.
30. European Medicines Agency. *Infanrix Hexa*. 2021; Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/infanrix-hexa.

31. Ladhani, S., et al., *Fall in Haemophilus influenzae serotype b (Hib) disease following implementation of a booster campaign.* Arch Dis Child, 2008. **93**(8): p. 665-9.
32. Morris, S.K., W.J. Moss, and N. Halsey, *Haemophilus influenzae type b conjugate vaccine use and effectiveness.* Lancet Infect Dis, 2008. **8**(7): p. 435-43.
33. Takala, A.K., et al., *Reduction of oropharyngeal carriage of Haemophilus influenzae type b (Hib) in children immunized with an Hib conjugate vaccine.* J Infect Dis, 1991. **164**(5): p. 982-6.
34. Barbour, M.L., et al., *The impact of conjugate vaccine on carriage of Haemophilus influenzae type b.* J Infect Dis, 1995. **171**(1): p. 93-8.
35. Mohle-Boetani, J.C., et al., *Carriage of Haemophilus influenzae type b in children after widespread vaccination with conjugate Haemophilus influenzae type b vaccines.* Pediatr Infect Dis J, 1993. **12**(7): p. 589-93.
36. Charania, N.A. and S.M. Moghadas, *Modelling the effects of booster dose vaccination schedules and recommendations for public health immunization programs: the case of Haemophilus influenzae serotype b.* BMC Public Health, 2017. **17**(1): p. 705.
37. Southern, J., et al., *Immunogenicity of a fourth dose of Haemophilus influenzae type b (Hib) conjugate vaccine and antibody persistence in young children from the United Kingdom who were primed with acellular or whole-cell pertussis component-containing Hib combinations in infancy.* Clin Vaccine Immunol, 2007. **14**(10): p. 1328-33.
38. Wang, Z., G. Rost, and S.M. Moghadas, *Delay in booster schedule as a control parameter in vaccination dynamics.* J Math Biol, 2019. **79**(6-7): p. 2157-2182.
39. Low, N., et al., *Comparing Haemophilus influenzae type b conjugate vaccine schedules: a systematic review and meta-analysis of vaccine trials.* Pediatr Infect Dis J, 2013. **32**(11): p. 1245-56.
40. World Health Organization, *Haemophilus influenzae type b (Hib) Vaccination Position Paper - July 2013.* Wkly Epidemiol Rec, 2013. **88**(39): p. 413-26.
41. Barug, D., et al., *Infant antibody levels following 10-valent pneumococcal-protein D conjugate and DTaP-Hib vaccinations in the first year of life after maternal Tdap vaccination: An open-label, parallel, randomised controlled trial.* Vaccine, 2020. **38**(29): p. 4632-4639.
42. Taranger, J., et al., *Vaccination of infants with a four-dose and a three-dose vaccination schedule.* Vaccine, 1999. **18**(9-10): p. 884-91.
43. Poolman, J., et al., *Clinical relevance of lower Hib response in DTPa-based combination vaccines.* Vaccine, 2001. **19**(17-19): p. 2280-5.

3.7 Invasive pneumococcal disease

### 3.7.1 History of vaccination against invasive pneumococcal disease

Pneumococcal vaccination was introduced in the NIP of The Netherlands in 2006, with the 7-valent pneumococcal conjugate vaccine (PCV7). Vaccination was provided with a "3+1 schedule", i.e., three primary doses at 2, 3 and 4 months of age and a booster dose at 11 months of age (Figure 1). In 2011, PCV7 was replaced with the 10-valent vaccine (PCV10). At the end of 2013, the 3+1 schedule was reduced to a 2+1

schedule at 2, 4 and 11 months after it was shown that the immunological response was not different from a 3+1 schedule [1]. Another change in the schedule was made in 2020 after the introduction of maternal pertussis vaccination: from then on PCV10 is provided at 3, 5 and 11 months of age, a schedule that showed good antibody immune responses in a Dutch clinical trial [1]. The uptake of PCV7 and subsequently PCV10 has been above 93% since the introduction. Besides the conjugate vaccines, there is also a 23-valent polysaccharide pneumococcal vaccine available (PPV23) that is recommended for medical risk groups [2]. Furthermore, since autumn 2020, PPV23 is recommended for the population aged 60 years and older. Due to vaccine shortages, vaccination is introduced per birth cohort. Individuals born in 1941-1947 were invited first (autumn 2020). The uptake of PPV23 was about 73% in this first year of introduction [3]. In autumn 2021, individuals born between 1948-1952 have been invited. PPV23 is not immunogenic in children below 2 years of age, nor does it affect carriage. Therefore, PPV23 is not an alternative for the conjugate vaccines used in the NIP.

3.7.2   *Goal of vaccination against invasive pneumococcal disease*
The main purpose of vaccination against *Streptococcus pneumoniae* is to prevent invasive pneumococcal disease (IPD) and pneumococcal pneumonia in infants and young children (aged < 5 years old). The secondary goal is to prevent invasive disease and pneumonia in the population aged 60 years and older. These aims can be achieved by a combination of individual and indirect protection.
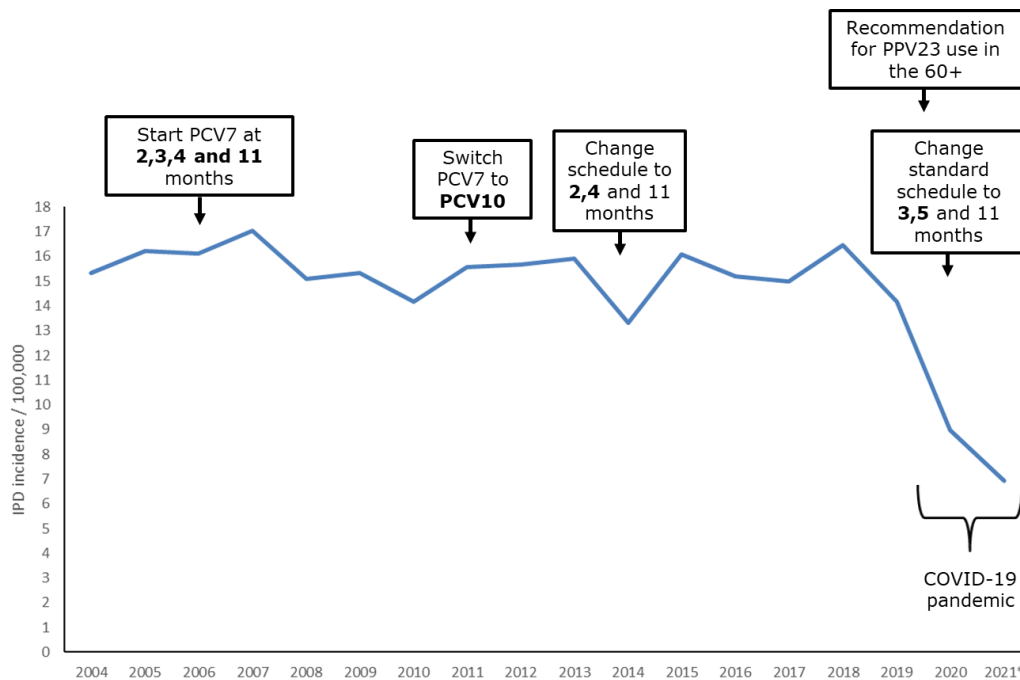
Figure 1 Changes in the pneumococcal vaccination strategy in relation to the all-serotype IPD incidence in the Dutch population (all age-groups). Data are based on isolates sent in from sentinel laboratories, that cover about 25% of the Dutch population.

3.7.3 Epidemiology of invasive pneumococcal disease in The Netherlands

Before introduction of vaccination in the NIP, the incidence of IPD was about 16 cases per 100,000. The highest incidence was seen among the population aged 60 years and older (around 50 per 100,000) and children under 5 years of age (12 per 100,000) (Figure 2). After PCV7 was introduced, the incidence of IPD decreased rapidly among children under five to 8 per 100,000 in 2008/2009 due to a decrease in disease caused by PCV7-serotype pneumococci (Figure 3) [4]. Because the incidence of non-PCV7 IPD increased as a result of serotype replacement, the overall IPD incidence in the under-fives slightly increased again from 2009-10 to 2011-12 but the incidence was still much lower compared to before PCV introduction (Figure 3) [4]. The positive net effect is related to the lower invasiveness of replacing serotypes, i.e., causing less often diseases in relation to the carriage frequency [5]. To prevent IPD caused by the replacing serotypes, PCV7 was substituted with PCV10 in 2011. The switch to PCV10 led to a further decrease in IPD to around 4 per 100,000 in the under-fives [4]. Not only invasive disease but also community acquired pneumonia decreased in this population [6]. However, the decrease was again slightly offset due to serotype replacement. The incidences in epidemiological year 2019/2020 and 2020/2021 were much lower than the previous years (Figure 1), most likely related to the non-pharmaceutical interventions against COVID-19, including social distancing and school closures [7, 8], although changes in testing behaviour/diagnoses cannot be ruled out entirely [9].
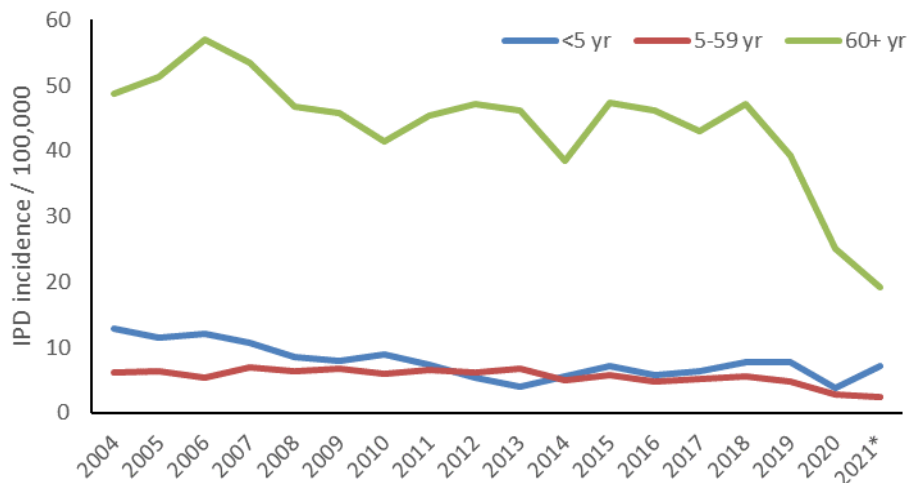

Figure 2 Incidence of IPD (all serotypes) by age groups for the period 2004-2021. Data for the age group <5 years is based on nation-wide surveillance, while data for 5-59 years and 60+ years are based on isolates sent in from sentinel laboratories, that cover about 25% of the Dutch population. For 2021, the data are extrapolated from data up to and including October 2021. Note that since 2020, COVID-19 control measures have been in place affecting the numbers.
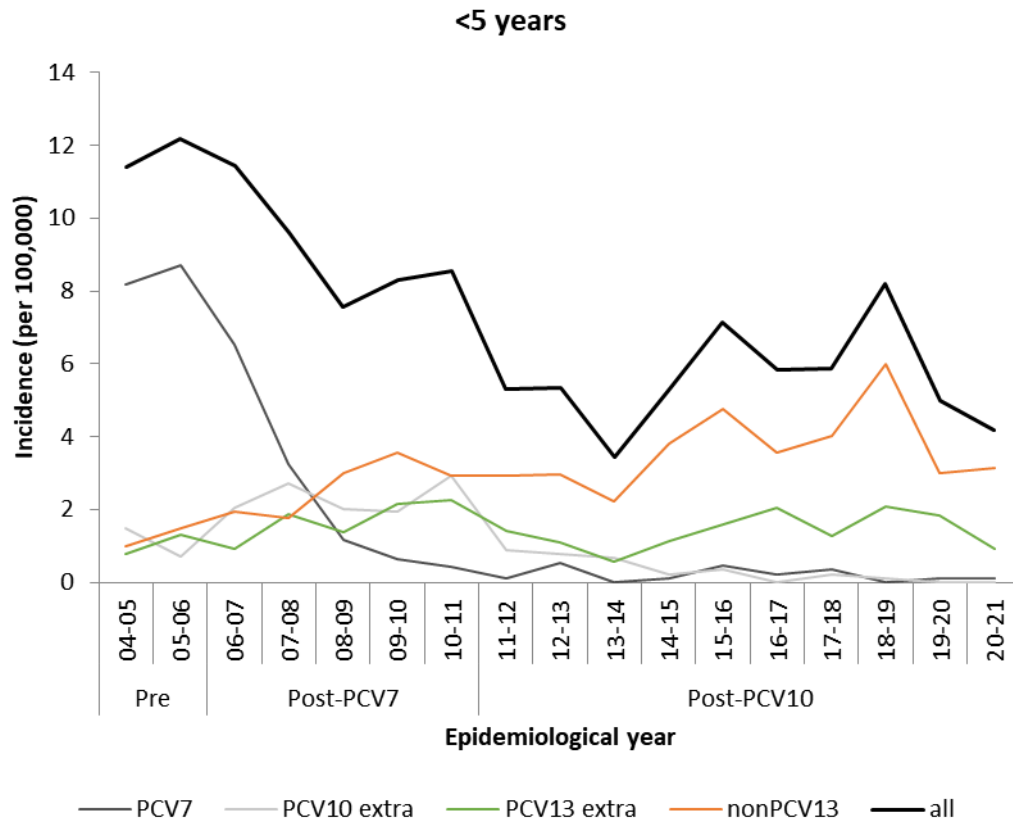
Figure 3 Incidence of IPD in children <5 years of age by vaccine serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes and non-PCV13 serotypes as well as IPD cases regardless of serotype), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005). National data covering all isolates of blood and/or liquor are included. Note that since 20-21, COVID-19 control measures have been in place affecting the numbers.

Besides the decrease in IPD incidence in the vaccinated age group from 12/100,000 pre-vaccination (2004-2005) to 6-8/100,000 in the three years before the COVID-19 pandemic, also a slight decrease in the incidence of IPD (Figure 2) and of community acquired pneumonia in other age groups was observed as a result of indirect protection [6]. Due to the simultaneous decrease in vaccine-type disease and increase in non-vaccine type disease, no further decrease in IPD incidence was observed after the switch to PCV10 (Figure 4). Similar to the under-fives, the incidence of IPD has been much lower since the COVID-19 pandemic (Figure 2).
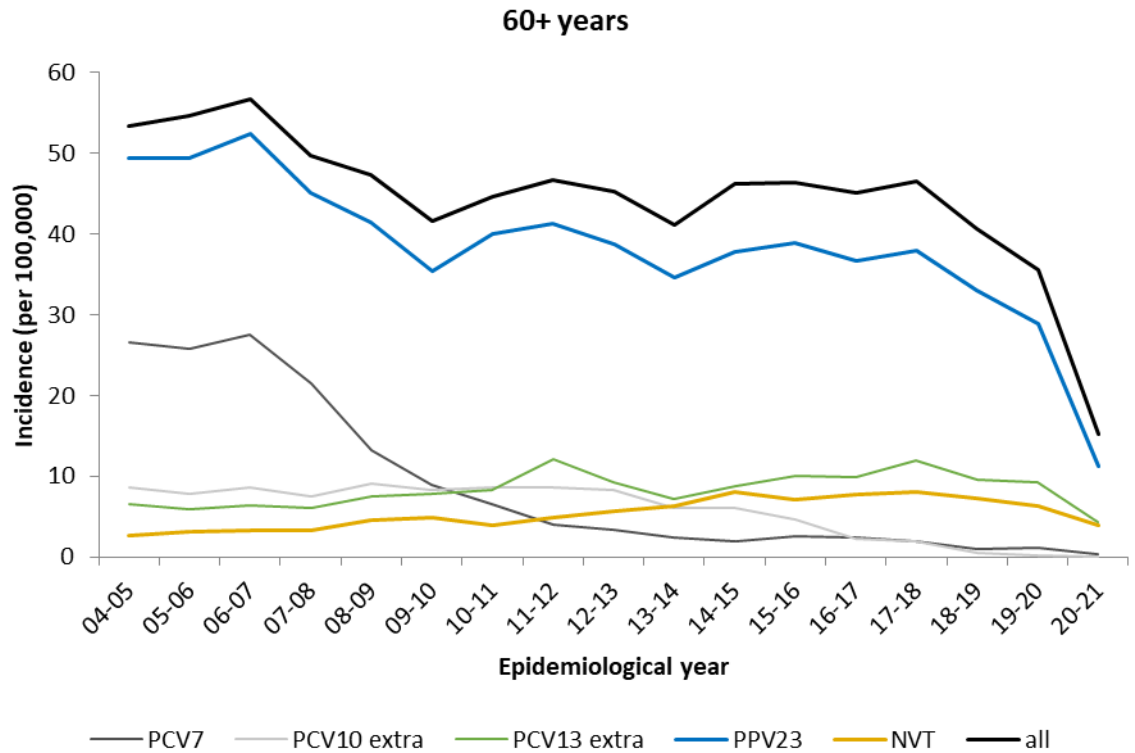
Figure 4 Incidence of IPD in older adults (60 years and older) by vaccine serotype as well as IPD cases regardless of serotype, presented by epidemiological year (e.g. 04/05 = June 2004-May 2005). Vaccine serotypes are divided as PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes, PPV23 serotypes (including PCV13 serotypes but not 6A) and non-vaccine serotypes (NVT; i,e, nonPCV13 and nonPPV23). Data are based on data from sentinel laboratories, which cover about 25% of the Dutch population. Note that since 20-21, COVID-19 control measures have been in place affecting the numbers.

As a result of the redistribution of serotypes after vaccine introduction, the proportion of cases and carried isolates that are covered by PCV10 has decreased [10]. Overall, the serotypes included in PCV10 covered 4% of the cases in the epidemiological years 2019-2021. The most common serotypes in that year were serotype 8 (22% of all cases), 19A (18%), 3 (9%), 22F (8%) and 6C (6%). Serotypes 3 and 19A are included in the PCV13 vaccine, whereas PPV23 covers all top 4 serotypes isolated from IPD cases. The serotype distribution differed slightly by age group but the ranking was the same (Figure 5).
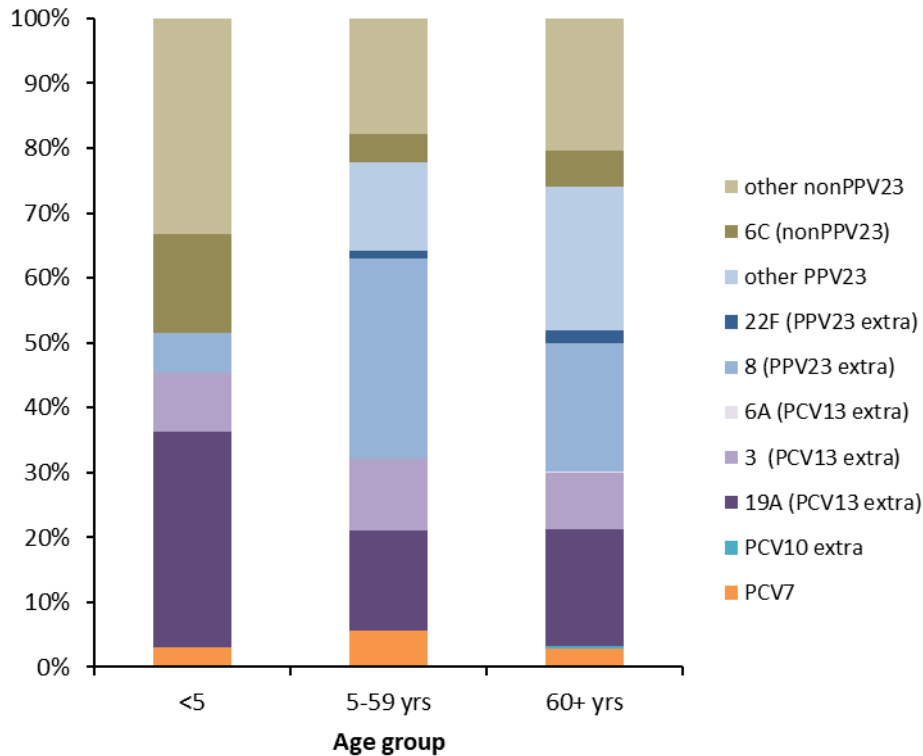
Figure 5 serotype distribution by age group for the epidemiological years 2019-2021. Data are obtained by 9 sentinel laboratories covering about 25% of the Dutch population. Overall, n=847 isolates were included, i.e., 32 for those <5 years, 188 for those aged 5-59 years and 627 for those aged 60+ years.

3.7.4   *Assessment of the vaccination against the six criteria, issues identified*
1. Is the protection adequate for all those intended to be protected?
Yes, direct and indirect protection against vaccine-type IPD is good.

Since the introduction of PCV7 in 2006, (only) 46 cases of vaccine-type IPD have been reported among vaccine-eligible children in the nationwide surveillance in The Netherlands. Of these, 23 children (50%) were considered vaccine failures, as the children were vaccinated with at least two doses with the second dose given at least two weeks before diagnosis. Serotype 19F was the most common serotype among vaccine failure cases (n=8, 35%), a serotype that has been described in relation to vaccine failure also in other countries [11]. The effectiveness of PCV10 in the Dutch schedule has been evaluated using the indirect cohort (or Broome) method, in which the odds of vaccination in vaccine-type IPD cases is compared with the odds of vaccination in non-vaccine-type IPD cases [4]. Up to and including May 2021, the effectiveness of PCV10 in the eligible population, i.e., being born since April 2006 and being aged 2 months or over was estimated at 87% (95%CI 68-95%) for at least two doses of PCV10.

In addition to the large direct effect of childhood vaccination, almost complete herd protection has taken place, thereby drastically decreasing the incidence of vaccine-type disease also among non-targeted age groups. A side effect of the vaccination programme is serotype replacement, i.e., an increase in colonization with non-vaccine

serotypes, that can cause disease. The incidence of non-vaccine type disease has therefore increased in those targeted by vaccination, as well as older age groups. However, overall, childhood vaccination has largely reduced the incidence of all-type IPD in those targeted and has slightly reduced the incidence of IPD in those not-targeted for vaccination. The amount of serotype replacement is related to the effectiveness of the programme but even more so, to the proportion of the carried serotypes that are covered by the vaccine. There are higher-valent pneumococcal conjugate vaccines available and being developed. The preventive potential of the currently used vaccine (PCV10) versus PCV13 may therefore be evaluated to determine whether a switch to PCV13, and/or in the future to a higher-valent vaccine, is beneficial.
There are no known problems with specific groups like prematurely born children and immunocompromised children.
Issue: Should the preventive potential of PCV10 versus PCV13 (or more valent PCVs in the future) be evaluated?

2. Is the applied vaccination strategy optimal?
Yes. Up to now, the use of PCVs in the NIP has been effective for the targeted and untargeted age-groups. The optimal schedule for the primary doses for PCV in the NIP has been studied in The Netherlands at the immunological level [1]. The study showed that the schedules with vaccination at 3 and 5 months and at 2, 4 and 6 months induce similar antibody immune responses and are superior compared to primary doses at 2,3 and 4 months. While the introduction of PCV7 started with a 3+1 schedule at 2, 3, 4 and 11 months which later changed to a 2+1 schedule at 2, 4 and 11 month as that schedule was shown not to be different immunologically from the 2, 3, 4 and 11 schedule, the schedule has been adapted to 3, 5 and 11 months in 2020. As shown above, the incidence of vaccine-type disease among the targeted age group is very low and the vaccine effectiveness is high [4].
Issues: None.

3. Does the programme include too much?
Maybe. Since January 2020 the UK infant pneumococcal immunisation programme consists of a 1+1 schedule with PCV13 doses given at 12 weeks and 12 months of age. Previously, the UK used a 2+1 schedule with PCV13. They argued, among others, that there is substantial indirect protection that will protect infants sufficiently [12]. They performed a modelling study predicting effects of the changed schedule for the entire population and showed that such change would have little impact on the occurrence of IPD and pneumococcal pneumonia [13]. The net effect would be the result from a slight increase in vaccine type disease and a slight decrease in non-vaccine type disease. The experience with the 1+1 schedule is still short, so we should follow the development of the IPD incidence in the UK.
Issue: Could a 1+1 schedule be applicable in The Netherlands?

4. Does the programme include too little?
Not concerning the number of doses, but maybe when focusing on the valency of the used vaccine. In 2013, the Health council concluded that it can be expected that PCV13 produces slightly greater direct health gains in infants and young children, especially with regard to 19A [14]. Indeed, due to the use of PCV10, the vaccine serotypes have now

almost been eliminated. Non-PCV10 serotypes are now more frequently the cause of IPD. The increase is among others seen in serotypes that are not covered by PCV10 but for which vaccination is available (e.g. serotype 19A -PCV13 serotype as well as serotype 6C that has shown to be partially covered through cross-protection from 6A in PCV13); serotype 19A was the most common cause of IPD in children under five in 2019-2021 (Figure 5). An evaluation of the preventive potential of PCV10 versus PCV13 may therefore be needed again.
Issue: Should the preventive potential of PCV10 versus PCV13 (or more valent PCVs in the future) be evaluated?

5. Is the timing of immunisations using combination vaccines optimal or at least acceptable?
There is no combination vaccine with non-pneumococcal antigens. However, PCV10 is administered at the same time as the DTaP-HBV-IPV/Hib (in the other arm), which, compared to other countries, is given quite early. There is no interference between the vaccines. If, for programmatic reasons, it would be desirable to postpone the booster vaccination a couple of months – to 12-15 months of age as is common in other countries –, no increase in IPD incidence is expected because of substantial herd protection already present.
Issue: The booster is given early compared to other countries. Could the booster dose be given at an older age if that would be desirable for programmatic reasons?

6. Are there important drawbacks of the NIP? For the population as a whole? For those who opt out? How are these drawbacks to be weighed against the advantages of the programme and its components?
Not concerning vaccine-type IPD. However, serotype replacement may reduce direct and indirect protection against IPD and pneumococcal pneumonia. The overall effect of the programme on the IPD incidence is still positive. Furthermore, the majority of the replacing serotypes are of lower invasiveness, and will therefore less often cause disease in healthy individuals, except for the high invasive serotypes 8 and 12F [5, 15]. However, members of specific risk groups such as e.g. those using immunosuppressive treatment [16], those suffering from haematological disorders [17], as well as other medium and high-risk groups [18], may still be susceptible to severe pneumococcal disease caused by these replacing serotypes. As PPV23 has recently been recommended for older adults, replacement disease will probably partly be prevented through direct protection by PPV23 in the older population.
Issue: Should the preventive potential of PCV10 versus PCV13 (or more valent PCVs in the future) be evaluated?

Encountered issues:
1. Could the booster dose be given at an older age if that would be desirable for programmatic reasons?
2. Does the virtual disappearance of vaccine types in the population open the possibility for a 1 + 1 schedule?
3. Should the preventive potential of PCV10 versus PCV13 (or more valent PCVs in the future) be evaluated?

3.7.5   *Exploration of the issues against the available knowledge*

Could the booster dose be given at an older age when this would be desirable for programmatic reasons?

The booster dose at 11 months is given quite early compared to several other countries (often at 12 or at 15 months) [19]. Although the direct and indirect effects on vaccine-type IPD are favourable, delaying the booster by one or more months may provide an even larger preventive effect based on a modelling study with Hib as example [20]. In several other countries with a 2+1 schedule with primary doses at 3 and 5 months (e.g. Scandinavian countries [19]), the booster is given at 12 months, which provides good (herd) protection [21, 22]. If for programmatic reasons it would be desirable to postpone the booster dose for several months, we do not expect any negative effects and maybe even some positive effects on direct and indirect protection against vaccine-type IPD.

Is a 1+1 schedule a valid option for The Netherlands?

In the UK, the primary series consists of a single PCV13 dose at 3 months, followed by a booster dose at 12 months. This simplification could be possible for The Netherlands as well if PCV10 vaccine coverage remains high and herd immunity is present. However, it is desirable to learn from the UK experience first.

An immunological study by Goldblatt at al. comparing a 1+1 schedule with a 2+1 schedule was conducted in the UK [23]. The study showed that for nine of the 13 serotypes in PCV13, post-booster responses in infants primed with a single dose were equivalent or superior to those seen following the standard UK 2+1 schedule while for four this was lower. The higher GMCs after the 1+1 schedule were seen for serotypes 1, 4, 14, and 19F. The lower GMCs after the 1+1 schedules were seen for serotypes 6A, 6B, 18C and 23F. Functional activity of antibodies was similar for both schedules but IgG antibody GMCs after the primary series were significantly lower after the 1+1 schedule for all serotypes except serotype 3. When analysed in relation to the generally used cut off as correlate of protection (0.35 µg/mL), a significantly greater proportion of children receiving a single priming dose were below the correlate of protection post-primary immunisation. This was specifically the case for serotype 6A (13% versus 84%), 6B (1% versus 34%), 9V (17% versus 79%) and 23F (6% versus 58%). Whether these changes have clinical relevance is not (yet) known. In The Netherlands, serotype 6A, 6B, 9V and 23F IPD did not occur among infants aged younger than 12 months since PCV10 introduction in 2011.

An observational study performed in Israel determined the vaccine effectiveness of a different number of primary doses on colonisation in children [24]. Such data may be used as proxy for whether or not herd protection can be expected. The study showed that receiving 2 primary PCV13 doses conferred 53% (95% confidence interval, 32–67%) protection against PCV13-serotype colonization at the age of ≤12 months. After one PCV13 dose, this was 14% (−13 to 36), i.e., a single primary dose was hardly protective against colonisation. For now, a 2+1 schedule seems most optimal, and it is worth waiting for data on the vaccine effectiveness in the population and on whether the level of herd

protection that has been obtained with the previous schedule, will be maintained.

Should the preventive potential of PCV10 versus PCV13 (or more valent PCVs in the future) be evaluated?
For prevention of IPD in children, two vaccines are currently available: the 10-valent PCV10 and the 13-valent PCV13. In The Netherlands, PCV10 is given as part of the NIP. PCV10 (as well as the previously used PCV7) has been very effective in preventing vaccine-type IPD.

PCV10 and PCV13 cover 10 similar serotypes: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, yet, PCV13 covers three extra serotypes: serotypes 3, 6A, 19A. Besides differences in serotypes, PCV10 and PCV13 differ in the used adjuvant and the conjugation. In PCV10, the capsular polysaccharide identifying the serotypes are absorbed to aluminium phosphate. Eight serotypes are conjugated to protein D, which is expressed by non-typeable *Haemophilus influenzae*, serotype 18C is conjugated to tetanus toxoid protein and 19F is conjugated to a diphtheria toxoid protein. In PCV13 the capsular polysaccharides are adsorbed to aluminium phosphate and all conjugated to the CRM197 protein.

Of all IPD cases, PCV10 covered 4% of all IPD cases in the epidemiological years 2019-2021, 28% of cases were covered by the three extra serotypes included in PCV13, 41% of cases were caused by serotypes covered by PCV20 but not PCV13 and 7% of cases were caused by the additional serotypes covered by PPV23. The proportions, however, differed between age groups (Figure 6). In the under-fives, PCV10 covered 3% of cases while PCV13 covers altogether 51%. The number of cases under-five years of age are small though (PCV10, n=1; PCV13extra, n=14, PCV20extra, n=3) and it should be noted that these proportions indicate the additional preventive potential of the vaccines; the low proportion of PCV10-type disease is a result of the large preventive effect that is already present.
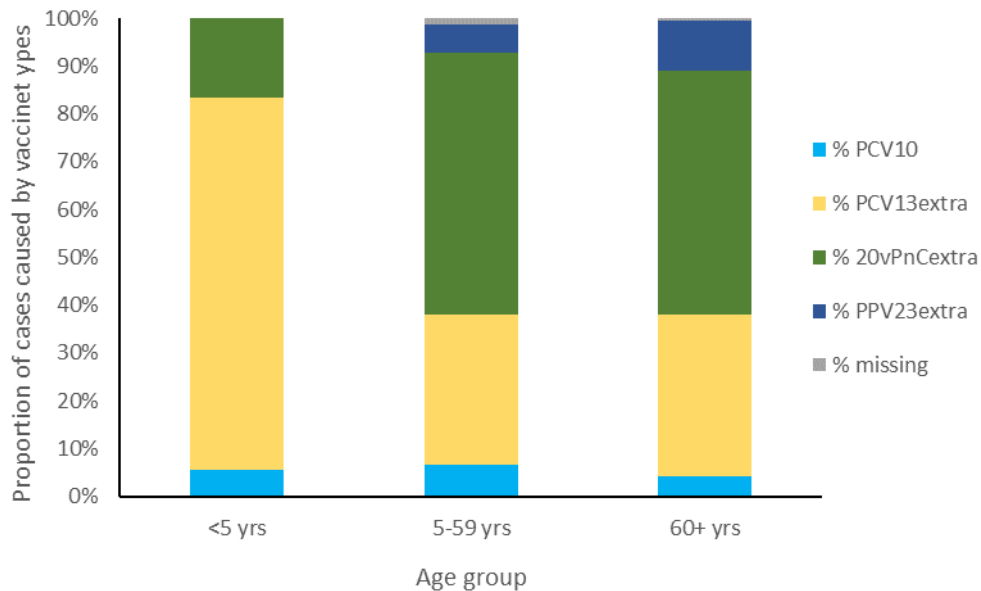
Figure 6 Vaccine-type distribution by age group for the epidemiological years 2019-2021. Data are obtained by 9 sentinel laboratories covering about 25% of the Dutch population. Overall, n=847 isolates were included, i.e., 32 for those <5 years, 188 for those aged 5-59 years and 627 for those aged 60+ years.

As shown in Figure 5, serotype 19A, serotype 3 and serotype 6C are now among the most common serotypes causing IPD in The Netherlands. Among under-fives, there were 11 serotype 19A cases, three serotype 3 cases and five serotype 6C cases. Although earlier it was hypothesised that there might be cross-protection of the serotype 19F antigen in PCV10 to serotype 19A IPD based on opsonophagocytosis studies [25, 26], this has not been the case; the vaccine effectiveness of PCV10 against 19A was estimated at 28% (95% confidence interval -179 – 81) [4]. PCV13 has good effectiveness against serotype 19A; in PCV13 countries, the 19A incidence decreased by 67-87% [27]. PCV13 seems not effective in preventing serotype 3 disease [27]. Serotype 6C may partly be prevented by PCV13 through cross-protection of the serotype 6A antigen [28]. The net effect of childhood vaccination with PCV7/10, i.e., the effect on the incidence of IPD caused by any serotype, was substantial for children in The Netherlands [4], with the incidence decreasing from 12/100,000 pre-vaccination to 8/100,000 in the pre-COVID-19 years (2018-2019). When looking at older age groups, the net effect was limited (50/100,000 to 43-47/100,000 pre-COVID-19). The incidence changes after PCV(10/13) use have been heterogenous world-wide, with some countries showing substantial decreases in the IPD incidence in all age groups while for other countries like The Netherlands, the incidence in non-targeted age groups returned (almost) to baseline [27, 29]; no clear differences in net effect have been observed between PCV10 and PCV13 countries [27]. Note that the recent introduction of PPV23 in older age groups in The Netherlands will directly prevent PPV23-type IPD in vaccinated adults.

Several higher-valent conjugated vaccines are in development: PCV15, 20vPnC and PCV24. PCV15 [30], produced by Merck, has already been

tested in phase three. The licence application of Pfizer for 20vPnC for the use in adults is already accepted in the US and is currently evaluated by EMA [31]. For the use of 20vPnC children, clinical trials are still ongoing [32] but licencing may already be possible in 2023/2024. The 24 valent vaccine (PCV24 of Merck) is under development in animals and licencing is not expected in the short term [33]. Besides these serotype-dependent vaccines, serotype independent vaccines such as protein vaccines, recombinant vaccines (live attenuated bacteria expressing pneumococcal antigens), inactivated whole cell vaccines (PATH-wSp) and combination vaccines (protein+conjugate or whole-inactivated influenza A + pneumococcal vaccines) are being developed [34]. The serotype independent vaccines currently still face considerable challenges and will not be available on the market for the coming years [35]. Furthermore, these are likely targeted towards medical risk groups only and not for use in the NIP. Generally, the use of higher-valent vaccines is expected to reduce the incidence of IPD caused by the included serotypes. However, similar as with lower-valent vaccines such as PCV10, colonization by non-vaccine serotypes is expected to increase. Whether or not this will result in more disease depends on the invasive capacity of the serotypes [5]. Up until now, several of the replacing serotypes are less invasive in healthy individuals [5, 10], but they may still cause disease in risk groups [17]. The recommendation of PPV23 vaccination among the 60+ partly reduces the need for indirect protection of this population as PPV23 covers the 10 serotypes that are covered by PCV10.

3.7.6   *Summary and conclusions; suggestions for the request for advice from the Health Council*
The current schedule effectively reaches its aim to prevent vaccine-type IPD in infants and young children (aged < 5 years old). An optimal schedule for the primary doses is used. The booster dose is given quite early compared to other countries. Although not an issue for the prevention of IPD in The Netherlands, it would be possible to postpone the booster vaccination several months if programmatic reasons would make that desirable.
A further reduction in the number of primary doses seems premature because of the limited experience with a 1+1 schedule. Given the level of herd protection still present from 2+1 vaccinated children it will take considerable time before any effects of such a change in vaccine schedule can be observed.
A down-side of the use of PCV is serotype replacement. IPD cases caused by serotypes that are currently predominant, most notably 19A and 6C, could be prevented by a switch to PCV13 or other multivalent vaccines. The Health Council may again want to discuss the added value of such a change.

3.7.7   *References*
1.   Spijkerman, J., et al., *Immunogenicity of 13-valent pneumococcal conjugate vaccine administered according to 4 different primary immunization schedules in infants: a randomized clinical trial.* JAMA, 2013. **310**(9): p. 930-7.
2.   National Institute for Public Health and the Environment (RIVM), *Vaccinatiegraad en jaarveslag Rijksvaccinatieprogramma Nederland 2020*. 2021.

3.   Heins, M., M. Hooiveld, and J. Korevaar, *Vaccinatiegraad Nationaal Programma Pneumokokkenvaccinatie Volwassenen 2020: monitor in het kort.* NIVEL, 2021.

4.   Peckeu, L., et al., *Impact and effectiveness of the 10-valent pneumococcal conjugate vaccine on invasive pneumococcal disease among children under 5 years of age in the Netherlands.* Vaccine, 2021. **39**(2): p. 431-437.

5.   Balsells, E., et al., *The relative invasive disease potential of Streptococcus pneumoniae among children after PCV introduction: A systematic review and meta-analysis.* J Infect, 2018. **77**(5): p. 368-378.

6.   van Deursen, A.M.M., et al., *Impact of infant pneumococcal conjugate vaccination on community acquired pneumonia hospitalization in all ages in the Netherlands.* Vaccine, 2017. **35**(51): p. 7107-7113.

7.   Brueggemann, A.B., et al., *Changes in the incidence of invasive disease due to Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis during the COVID-19 pandemic in 26 countries and territories in the Invasive Respiratory Infection Surveillance Initiative: a prospective analysis of surveillance data.* Lancet Digit Health, 2021. **3**(6): p. e360-e370.

8.   Middeldorp, M., et al., *Short term impact of the COVID-19 pandemic on incidence of vaccine preventable diseases and participation in routine infant vaccinations in the Netherlands in the period March-September 2020.* Vaccine, 2021. **39**(7): p. 1039-1043.

9.   Dirkx, K.K.T., et al., *The drop in reported invasive pneumococcal disease among adults during the first COVID-19 wave in the Netherlands explained.* Int J Infect Dis, 2021. **111**: p. 196-203.

10.   Vissers, M., et al., *Increased carriage of non-vaccine serotypes with low invasive disease potential four years after switching to the 10-valent pneumococcal conjugate vaccine in The Netherlands.* PLoS One, 2018. **13**(3): p. e0194823.

11.   Oligbu, G., et al., *Pneumococcal conjugate vaccine failure in children: A systematic review of the literature.* Vaccine, 2016. **34**(50): p. 6126-6132.

12.   Ladhani, S.N., N. Andrews, and M.E. Ramsay, *Summary of evidence to reduce the two-dose infant priming schedule to a single dose of the 13-valent pneumococcal conjugate vaccine in the national immunisation programme in the UK.* Lancet Infect Dis, 2021. **21**(4): p. e93-e102.

13.   Choi, Y.H., N. Andrews, and E. Miller, *Estimated impact of revising the 13-valent pneumococcal conjugate vaccine schedule from 2+1 to 1+1 in England and Wales: A modelling study.* PLoS Med, 2019. **16**(7): p. e1002845.

14.   Health Council of the Netherlands, *Vaccination of infants against pneumococcal infections (3)*. 2013.

15.   Amin-Chowdhury, Z., et al., *Characteristics of Invasive Pneumococcal Disease Caused by Emerging Serotypes After the Introduction of the 13-Valent Pneumococcal Conjugate Vaccine in England: A Prospective Observational Cohort Study, 2014-2018.* Clin Infect Dis, 2020. **71**(8): p. e235-e243.

16. Steens, A., et al., *Indirect Effects of Pneumococcal Childhood Vaccination in Individuals Treated With Immunosuppressive Drugs in Ambulatory Care: A Case-cohort Study.* Clin Infect Dis, 2019. **68**(8): p. 1367-1373.

17. Garcia Garrido, H.M., et al., *Invasive pneumococcal disease among adults with hematological and solid organ malignancies: A population-based cohort study.* Int J Infect Dis, 2021. **106**: p. 237-245.

18. Winje, B.A., et al., *The Risk of Invasive Pneumococcal Disease Differs between Risk Groups in Norway Following Widespread Use of the 13-Valent Pneumococcal Vaccine in Children.* Microorganisms, 2021. **9**(8).

19. European Centre for Disease Prevention and Control. *Vaccine Scheduler*. 2021; Available from: https://vaccine-schedule.ecdc.europa.eu/.

20. Wang, Z., G. Rost, and S.M. Moghadas, *Delay in booster schedule as a control parameter in vaccination dynamics.* J Math Biol, 2019. **79**(6-7): p. 2157-2182.

21. Steens, A., et al., *Prompt effect of replacing the 7-valent pneumococcal conjugate vaccine with the 13-valent vaccine on the epidemiology of invasive pneumococcal disease in Norway.* Vaccine, 2013. **31**(52): p. 6232-8.

22. Galanis, I., et al., *Effects of PCV7 and PCV13 on invasive pneumococcal disease and carriage in Stockholm, Sweden.* Eur Respir J, 2016. **47**(4): p. 1208-18.

23. Goldblatt, D., et al., *Pneumococcal conjugate vaccine 13 delivered as one primary and one booster dose (1 + 1) compared with two primary doses and a booster (2 + 1) in UK infants: a multicentre, parallel group randomised controlled trial.* Lancet Infect Dis, 2018. **18**(2): p. 171-179.

24. Lewnard, J.A., N. Givon-Lavi, and R. Dagan, *Dose-specific Effectiveness of 7- and 13-Valent Pneumococcal Conjugate Vaccines Against Vaccine-serotype Streptococcus pneumoniae Colonization in Children.* Clin Infect Dis, 2020. **71**(8): p. e289-e300.

25. Jakobsen, H., et al., *Pneumococcal serotype 19F conjugate vaccine induces cross-protective immunity to serotype 19A in a murine pneumococcal pneumonia model.* Infect Immun, 2003. **71**(5): p. 2956-9.

26. Robbins, J.B., et al., *Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups.* J Infect Dis, 1983. **148**(6): p. 1136-59.

27. Knoll, M.D. and on behalf of the PSERENADE Team, *Conclusions from the PSERENADE Project: Implications for Pneumococcal Vaccine Policy and What is Happening Next*, in *Meningitis Research Foundation Conference*. 2021.

28. World Health Organization, *Strategic Advisory Group of Experts (SAGE) on Immunizations PCV Working Group (WG). Pneumoccal Conjugate Vaccine (PCV) Review of Impact Evidene (PRIME). Summary of Findinds from Systematic Review*. 2017.

29. Hanquet, G., et al., *Effect of childhood pneumococcal conjugate vaccination on invasive disease in older adults of 10 European countries: implications for adult vaccination.* Thorax, 2019. **74**(5): p. 473-482.

30. Platt, H.L., et al., *A Phase II Trial of Safety, Tolerability and Immunogenicity of V114, a 15-Valent Pneumococcal Conjugate Vaccine, Compared With 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants.* Pediatr Infect Dis J, 2020. **39**(8): p. 763-770.

31. Pfizer. *EUROPEAN MEDICINES AGENCY ACCEPTS PFIZER'S MARKETING AUTHORIZATION APPLICATION FOR ITS INVESTIGATIONAL 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE FOR ADULTS 18 YEARS OF AGE OR OLDER*. 2021; Available from: https://www.pfizer.com/news/press-release/press-release-detail/european-medicines-agency-accepts-pfizers-marketing.

32. U. S. National Library of Medicine. *ClinicalTrials.gov: Studies found for Prevnar 20*. 2021; Available from: https://clinicaltrials.gov/ct2/results?cond=&term=Prevnar+20&cntry=&state=&city=&dist=.

33. McGuinness, D., et al., *Immunogenicity of PCV24, an expanded pneumococcal conjugate vaccine, in adult monkeys and protection in mice.* Vaccine, 2021.

34. Briles, D.E., et al., *Pneumococcal Vaccines.* Microbiol Spectr, 2019. **7**(6).

35. Alderson, M.R., *Status of research and development of pediatric vaccines for Streptococcus pneumoniae.* Vaccine, 2016. **34**(26): p. 2959-2961.

3.8   Invasive meningococcal disease

3.8.1   *History of vaccination against invasive meningococcal disease*
To protect against invasive meningococcal disease (IMD), meningococcal polysaccharide vaccines have been available since the 1970s, but these are not effective in young children. Conjugate meningococcal vaccines, where the purified meningococcal capsular polysaccharides are conjugated to a bacterial carrier protein, have been available since 1999; first a monovalent vaccine against meningococcal serogroup C (MenC) disease but nowadays, conjugate vaccines against serogroup A, C, W and Y (MenACWY) are available. In 2002, MenC vaccination was introduced in the Dutch NIP among 14-month-olds after an increase in the incidence of IMD serogroup C (IMD-C) (Figure 1). The introduction of MenC vaccination among 14 month-olds was accompanied by a catch-up campaign for those 1-18 years old. After an increase in IMD-W, a MenACWY vaccination campaign was performed among the 14-18-year olds (birth cohort 2001-2005) in 2018-2019 [1]. Furthermore, the MenC vaccination in the NIP at 14 months old was replaced with MenACWY vaccination in 2018. From 2020 onwards, MenACWY vaccination is routinely given to 14-year-olds in the NIP. Although Nimenrix®, Menveo® and MenQuadfi are all licensed MenACWY vaccines for use in The Netherlands [2], only Nimenrix has been used in the NIP up to 2021. From March 2022, the 14-month dose will become MenQuadfi instead of Nimenrix.

Both monovalent MenC and quadrivalent MenACWY vaccines effectively protect against vaccine-type IMD, with a vaccine effectiveness of 87% (95%CI 77-93) and 69% (95%CI 51-80), respectively, estimated in a meta-analysis ([3]; note, for MenACWY only one study, from the USA, was included [4]). The successful MenACWY vaccination campaign in The Netherlands had a vaccine uptake estimated at 86% in 14-18-year-olds. Here, the vaccine effectiveness of MenACWY against IMD-W in toddlers eligible for vaccination was estimated for the period July 2019-March 2020 to be 92% (95%CI -20-99.5) [5, 6]. Among teenagers that were eligible for vaccination, no IMD-W cases occurred and the vaccine effectiveness could therefore not be determined. Since the MenACWY vaccination campaign was finished, only two (IMD-W) cases occurred among individuals eligible for vaccination, of which one of the cases had been vaccinated with MenACWY and one was unvaccinated; both cases were two years old. The higher vaccine effectiveness for MenACWY estimated in the Dutch compared to the USA study, may be explained by the longer follow up in the USA study as the vaccine effectiveness decreased with time since vaccination, furthermore, different vaccines were used which may be another explanation (MenACWY diphtheria toxoid conjugate vaccine compared to MenACWY tetanus toxoid conjugate vaccine) [4].

Since the end of 2014 there are protein vaccines available that protect against IMD-B: 4CMenB (Bexsero) and MenB-fHbp (Trumenba) of which Bexsero can be used from infants-age and Trumenba from adolescents age. In 2018, the Health council advised against the introduction of MenB vaccination in the NIP because of the uncertainties concerning its effectiveness and the unfavourable cost-effectiveness ratio as well as high fever after vaccination in very young children leading to hospital admissions [7].
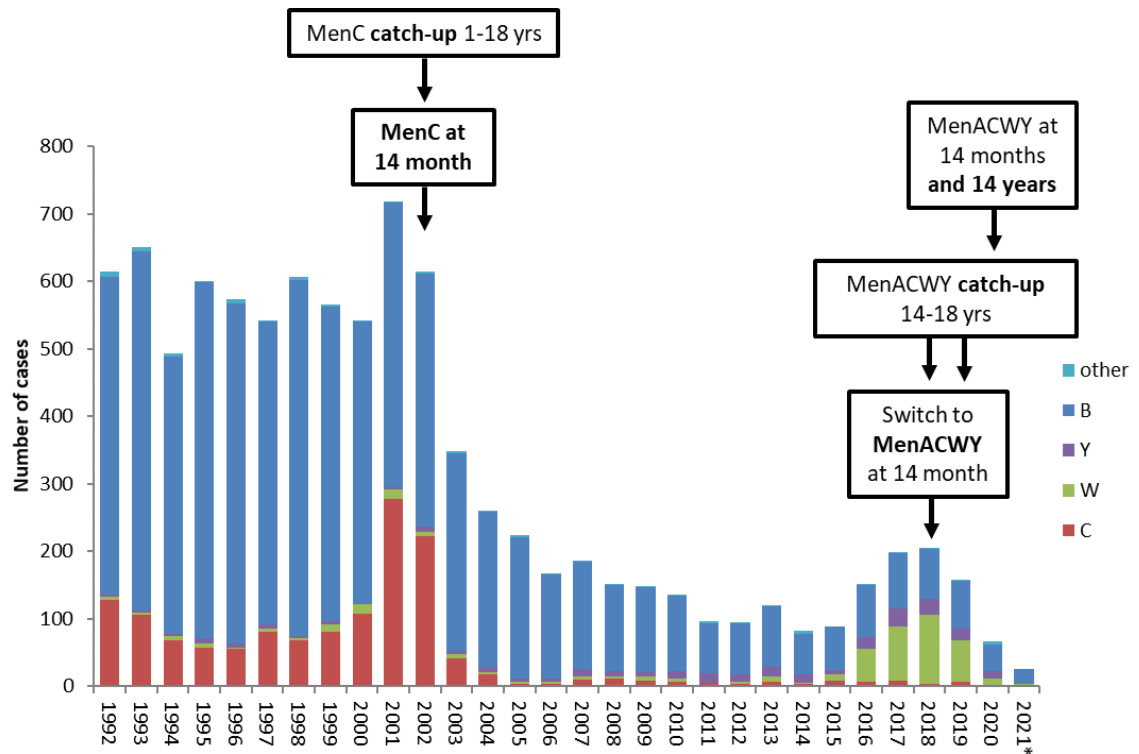
Figure 1 The number of invasive meningococcal disease (IMD) cases by serogroup for the period 1992-september 2021 and the timing of vaccine introductions or catch-up campaigns. Note that the numbers for 2021 are expected to rise as the bar does not include a full year yet.

3.8.2   *Goal of vaccination against invasive meningococcal disease*
The primary objective is to prevent invasive meningococcal disease of those serogroups included in the NIP schedule in children up to 5 years of age and in adolescents and young adults. The secondary objective of the programme is to indirectly protect other age groups through reduction of circulation of vaccine-type meningococci.

3.8.3   *Epidemiology of invasive meningococcal disease in The Netherlands*
Before the introduction of MenC vaccination in 2002, the overall incidence of IMD fluctuated around 4 cases per 100,000 inhabitants in The Netherlands. Most IMD cases (~80%) were caused by serogroup B followed by serogroup C (~15%). The number of IMD-C cases rose in 2000-2002 from around 70 per year in 1994-1999 to 222 in 2002 (Figure 1), which prompted the introduction of MenC vaccination in the NIP. This vaccine implementation, together with a (natural) decrease in IMD-B, resulted in a decrease in all-serogroup IMD from around 600 cases before 2003 to 175 (incidence 1/100,000) in 2006 and declined further to around 100 cases yearly (incidence 0.6/100,000) in 2011-2015. The number of IMD-C cases decreased to less than 10 per year. Since 2016, however, the number of all-serogroup IMD increased to 206 (incidence 1.2/100,000) in 2018 as a result of an increase in IMD-W. While up to 2015 only 10-15 cases of IMD-W occurred yearly, this increased to 103 cases in 2018. As IMD-W is vaccine-preventable, the MenACWY catch-up campaign was performed and a switch to the

tetravalent MenACWY vaccine was implemented in the NIP [1]. After the campaign, the number of IMD-W cases decreased abruptly. Of the other MenACWY serogroups, IMD-A has not been reported in The Netherlands since 2004. No IMD-C cases occurred in 2020-2021. IMD-Y has been uncommon in The Netherlands (15-25 cases per year), but this decreased to 10 cases in 2020 and zero cases in 2021. Note that these recent decreases in the number of IMD-ACWY cases are at least also partly caused by the control measures against SARS-CoV-2 [8]. This preventive effect of the COVID-19 control measures is reflected in the decrease in IMD-B, from around 75 cases in the years 2011-2018 (incidence 0.40-0.45/100,000) to 40 cases in 2020 (0.23/100,000) and 21 (0.16/100,000) up to and including September 2021.

Meningococci are commonly carried in the throat, from which transmission can take place. Through prevention of meningococcal carriage, transmission can be prevented thereby enhancing herd protection. Both, MenC and MenACWY are effective in protecting vaccine-type IMD, additionally, for monovalent MenC vaccination results show effective prevention of pharyngeal carriage but for MenACWY the results were non-significant [3]. After the Dutch switch to MenACWY with its catch-up campaign, the incidence of IMD in non-targeted age groups decreased by 57% (34-72) from July 2017-March 2018 compared to July 2019-March 2020 [5] (Figure 2), which is suggestive of indirect protection. Similarly, during the COVID-19 period (2020-2021), the overall incidence of IMD-ACWY decreased more than the incidence of IMD-B (Figure 1), which also indicates indirect effects of vaccination. Because of the study design it cannot be excluded that other factors including natural fluctuation and serogroup-specific susceptibility for COVID-19 control measures may play a role in the decrease. Because of the COVID-19 pandemic, the slightly longer term direct and indirect effects cannot yet be determined.
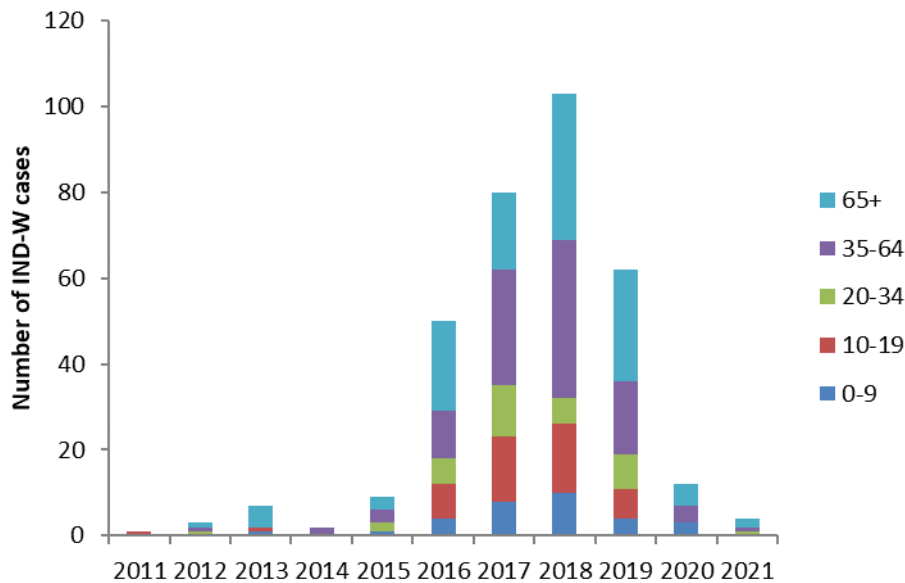
Figure 2 Age-specific number of invasive meningococcal disease serogroup W (IMD-W) cases for the period 1992-September 2021 and the timing of vaccine introductions or catch-up campaigns. Note that the numbers for 2021 are expected to rise as the bar does not include a full year yet.

3.8.4   *Assessment of the vaccination against the six criteria, issues identified*
Criterion 1. Is the protection adequate for all those intended to be protected?
Yes. Since vaccine introduction and the accompanied catch-up campaigns, the number of vaccine-type IMD cases has decreased substantially. The vaccine effectiveness was estimated at 92% (95%CI - 20-99.5) [5]. For teenagers no vaccine effectiveness estimate could be obtained as no IMD-W cases occurred among those eligible for vaccination. Although the SARS-CoV-2 epidemic affects the evaluation of the change from MenC to MenACWY vaccination, the programme seems to protect those targeted for vaccination and there are indications that indirect protection also takes place [5].

Among immunocompromised individuals such as asplenic patients, a lower percentage seroconverts after vaccination and they have lower quality antibodies upon vaccination [9]. As far as is known, there are no problems with the protection of specific paediatric groups such as prematurely born children or immunocompromised children, although the low incidence of the chronic conditions and of IMD complicates the evaluation in these groups. As the first MenACWY vaccination is offered at 14 months, the prematurity of the immune system of prematurely born children is less likely to play a role.
Issues: None

Criterion 2.   Is the applied vaccination strategy optimal?
Yes, the applied vaccine strategy has been effective in preventing IMD caused by ACWY serotypes; few IMD-C, IMD-W and IMD-Y cases have been observed in recent years. Likely irrespective of vaccination, IMD-A has not caused any case in The Netherlands since 2004. Furthermore, inclusion of the MenACWY vaccination at the age of 14 years is expected

to establish herd protection by reducing carriage. Such indirect effect was seen after the catch-up campaign for MenC vaccination ([10]; Figure 2), and was suggested by the recent data of MenACWY despite its challenges due to the COVID-19 pandemic and natural fluctuation [5]. The indirect effect of MenACWY vaccination may, however, be slightly less because of the lower or more uncertain vaccine effectiveness [3, 5]. No replacement by non-vaccine serogroups has occurred after introduction of MenC vaccination and this is also not seen nor expected after introduction of MenACWY vaccination.
Issues: None

Criterion 3. Does the programme include too much?
No (not yet?). The direct effect of the 14-months-dose and the 14-years-dose work well against IMD-ACWY (Figure 1 and 2). Besides the direct effects, it is expected that vaccination at 14 year olds with the MenACWY vaccine will increase indirect protection, i.e. the incidence of IMD in non-vaccinated age groups will also decrease as a result of a decrease in meningococcal carriage. The effect of MenACWY on vaccine-type carriage is, however, still inconclusive; a meta-analysis showed a small but non-significant reduction (vaccine effectiveness against carriage: 12%, 95%CI -18 - 34) [3]. The Dutch results of the MenACWY campaign suggest indirect protection but the study design does not allow for causal inference [5]. It might therefore be expected that MenACWY carriage will be decreased in adolescents/students with the 14-year dose. Provided that substantial indirect effects of the 14 year dose protect non-vaccinated age groups in the coming years, a possibility of omitting the 14-months booster vaccination dose may be evaluated as those may then already be protected indirectly.
Issues: Will it in the future be possible to omit the 14-months dose?

Criterion 4. Does the programme include too little?
No. MenACWY vaccination prevents vaccine-type IMD well with the current programme. For the included serogroups, the programme therefore does not include too little. However, the programme does not protect against IMD-B. There are two vaccines available that protects against IMD-B (4CMenB, Bexsero and MenB-fHbp, Trumenba), however, due to the nature of the vaccines, being protein-based instead if polysaccharide-based, the protection depends on the coverage of the strains circulating within a country. For The Netherlands, the strain coverage of 4CMenB is estimated at around 73% for all isolates in the years 2017-2019 and 58% for children aged 0-4 years, but the strain coverage depended on the clone and the age groups [11]. MenB vaccination has been shown effective in preventing IMD-B (vaccine effectiveness 65%, 95%CI 52-75; mainly in adolescents) but does not affect MenB carriage (vaccine effectiveness between 2% and -12%) [3]. In infants, the effectiveness of the 2+1 schedule was estimated at 53% (95%CI -34 - 83) overall and at 73% against IMD-B caused by 4CMenB-covered strains [12]. MenB vaccination is planned to be evaluated by the Health Council in 2022 and will not be included in this evaluation.
Issues: Not for this document

Criterion 5. Is the timing of immunisations using combination vaccines optimal or at least acceptable?

Yes. The conjugated MenACWY vaccine requires several doses when given before the age of 1 year old. However, one dose at 14-months is enough to provide protection, but leaves the child unprotected prior to the vaccination. Inclusion of the dose at 14 years seems very effective in the targeted age group and likely provides indirect protection. The vaccination provided at age of 14 years may, however, be given one or two years earlier if required/desired for the programme, albeit at the cost of a reduction in immunity and duration of protection and likely of indirect protection. If the timing of the 14-year dose would be adjusted, it is important to take into account that those that carry and likely transmit meningococci most, i.e., around 18-19 years [13-15] are (still) protected through vaccination, to keep both the direct and indirect protection adequate.

Issues: Could the second dose be given at an earlier age, when that would be desirable for programmatic reasons?

Criterion 6. Are there important drawbacks of the NIP? For the population as a whole? For those who opt out? How are these drawbacks to be weighed against the advantages of the programme and its components?

No. For meningococci, serogroup replacement, as seen with pneumococci, has not been observed, so the net result of vaccination is not diminished through replacement.

Issues: None

Encountered issues:

Vaccination with MenACWY effectively prevents vaccine-type IMD and there are no clear disadvantages. The encountered issues are mainly focused on future developments and the vaccination strategy.

- If the MenACWY vaccination coverage for 14-years olds would be high enough and would provide (nearly) complete herd protection, vaccination at 14 months might be omitted. Note, this is not yet the case and because of the fulminant character of IMD and the uncertainties concerning the extent of herd protection, such change would yet be preliminary.
- Could the second dose be given earlier, when programmatic reasons would make that desirable?
- MenACWY invasive disease has become uncommon. Most IMD cases are now caused by serogroup B. Protein vaccines that provide protection against IMD-B are available but not included in the NIP. The health council will advise in 2022 on MenB vaccination [7], so this issue will not be discussed here comprehensively.

3.8.5   *Exploration of the issues against the available knowledge*

Will the 14-year dose provide enough herd protection so that the 14 months dose may be omitted in the future?

The conjugated meningococcal polysaccharide vaccines require several doses to be effective in infants younger than 1 year. The moment of the first vaccination in the NIP, at 14 months of age, seems therefore efficient (only one dose) and effective; IMD-ACWY is rare before the age of 14 months (Figure 3). Before MenC vaccination was introduced at 14

months, around 10-20 infant cases occurred yearly, which has decreased to 0-2 cases yearly since MenC vaccine introduction. Since the switch to MenACWY and the catch-up campaign (2019 onwards), 0-2 cases IMD-ACWY cases per year have occurred before 14 months of age (IMD-W and IMD-Y). The direct effect of the dose at 14-months-olds, together with indirect protection induced by the programme, seems to protect toddlers effectively against IMD-ACWY.
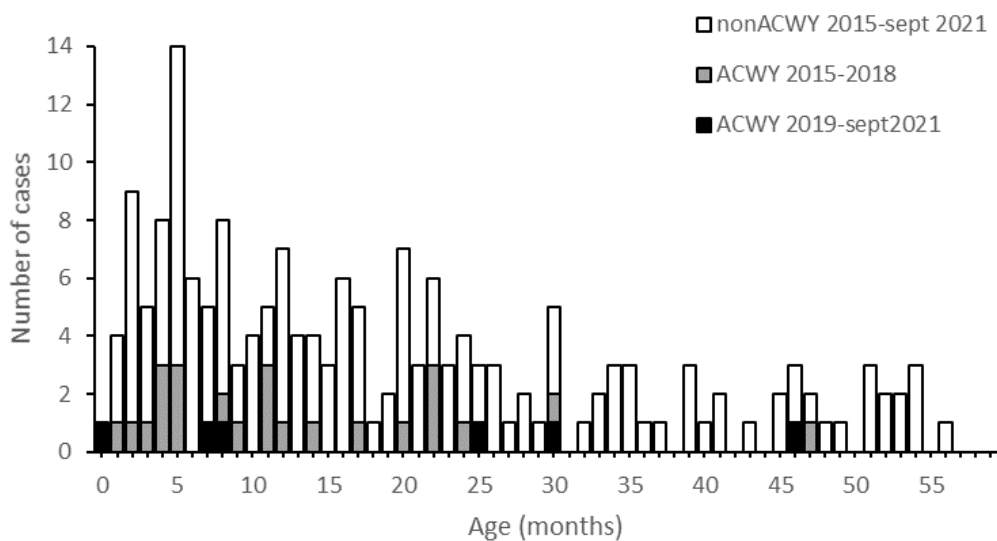

Figure 3 Number of invasive meningococcal disease cases younger than 5 years of age caused by serogroup A, C, W or Y (ACWY) in the period the period 2015-2018 (grey; n=24) and 2019-september 2021 (black; n=6) and by non-ACWY serogroups in 2015-september 2021 (white; n=150) by age in month. Note that the numbers for the period 2019-september 2021 are affected by both, the MenACWY vaccination campaign and by the COVID-19 pandemic. Among the IMD-ACWY cases, one case at 30 month of age had been vaccinated with MenACWY, i.e., was a vaccine failure; no vaccine failures occurred in this period for MenC.

If herd immunity would be present, toddlers would already be protected indirectly and the 14-months-dose would be redundant. If the 14-months MenACWY dose would be removed, children younger than 14 years old will then no longer be protected directly through individual vaccination so herd protection should then be (almost) complete. IMD is an unpredictable and fulminant disease that fluctuates over time and between countries, which makes the evaluation of the amount of herd protection, and therefore such decision, challenging. An additional complication is that current herd protection to children under the age of 14 months may be the combined herd-effect of the vaccination at 14 years and 14 months, as mingling of children under the age of 14 months with children aged over 14 months in e.g. day care facilities is common. Longer term follow-up of meningococcal vaccine uptake and IMD-ACWY will therefore be needed after the COVID-19 preventive measures have been lifted, to determine the effect of the dose at 14 years on the meningococcal epidemiology in The Netherlands. Note that in several other countries, like in the UK, Greece, Austria, Italy [16], MenACWY vaccination is only provided at adolescents age. In UK, MenACWY vaccination at adolescent age replaced the MenC booster at

that age in 2015 after an increase in IMD-W. The incidence of IMD-W has since decreased in UK [17]. The incidences of IMD-ACWY are reported to be lower in Greece, Austria and Italy compared to The Netherlands [17].

Another aspect with omitting the 14-months-dose is that the 14-years-dose will no longer be a booster dose but becomes the primary dose. Although studies show good immunological responses after single adolescent doses [18, 19], it needs to be followed up whether the duration of protection will be affected by being a single versus booster dose.

Seroprevalence data can be useful in relation to this issue, to determine the immunological status of the population. The most recent serological survey performed in The Netherlands was performed in 2016-17 (Pienter 3) [20]. This was 15 years after introduction of the MenC conjugate vaccination in the NIP alongside a large mass vaccination campaign for all children 1-18 years of age, but before the introduction of MenACWY vaccination at 14 years of age. Note that the seroprevalence data do not only reflect immunological responses to vaccination, but also to natural boosting as long as the serogroup is present in the population. Pienter 3 showed a slight increase in MenC-polysaccharide (PS)-specific geometric mean concentrations (GMCs) in 14-23-month-olds (orange line in Figure 4), compared to the serosurvey from 10 years earlier (Pienter 2; blue line in Figure 4) . In the 2016-17 serosurvey, MenC PS GMCs gradually declined in children from 2 years of age until 6 years of age from 0.93 µg/mL to 0.18 µg/mL. In children older than 6 years, low MenC-PS specific GMC levels were observed throughout childhood until the age of 17-18 years, indicating waning of immunity after the infants-dose. While the largest peak in GMC in 2006-07 was observed in 19-20-year-olds, in 2016-17 the peak was observed in 26-30-year-olds, albeit lower than ten years ago. This age group is comprised of individuals that were vaccinated 15 years prior to serum collection in this study, with a single MenC vaccination given at an age of 17-18 years, during the mass campaign in 2002. The results are therefore suggestive of waning immunity after the adolescents dose. In adults aged 31 years and older, a group that has not been eligible for vaccination, the GMCs are low.
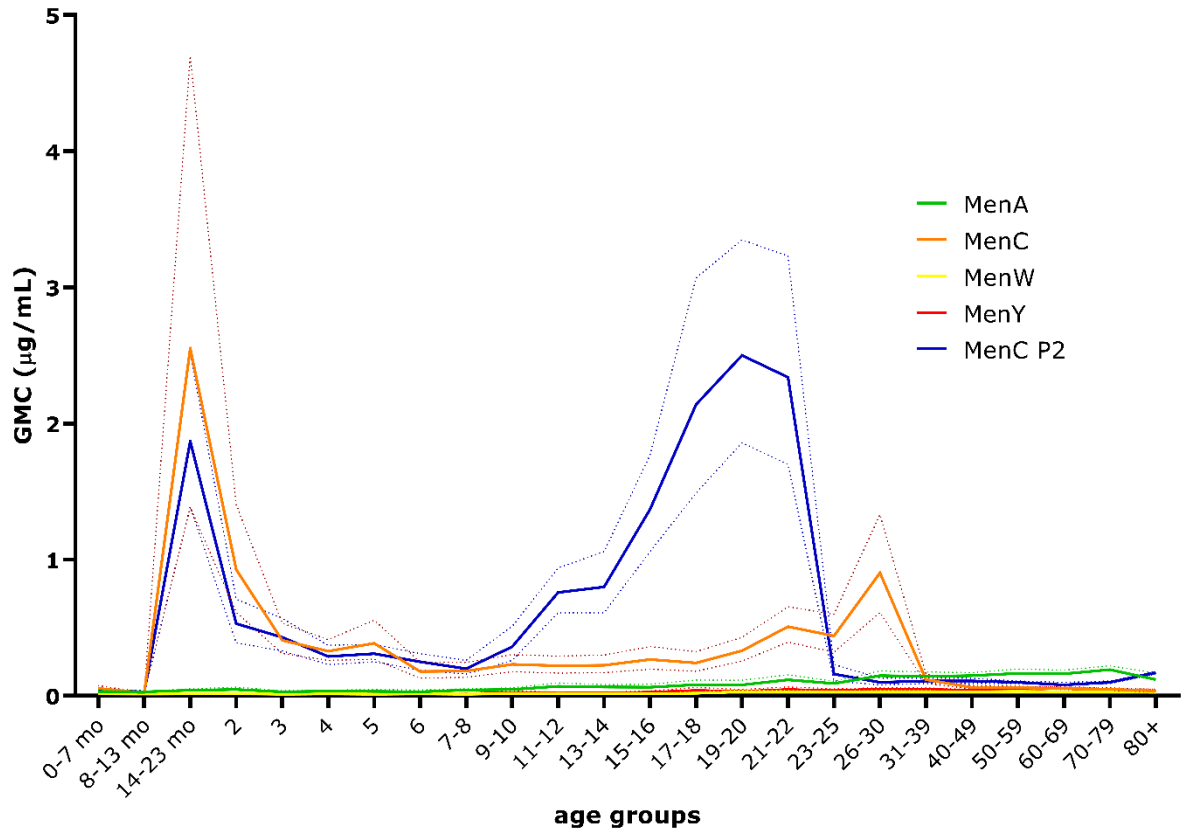
Figure 4 Polysaccharide (PS)-specific geometric mean concentrations (GMCs) with 95% confidence intervals (light colours) against MenC-PS measured in 2006-07 (Pienter 2-study; in blue) and 2016-17 (Pienter 3-study; in orange), as well as GMCs against MenA-PS (green), MenW-PS (yellow) and MenY-PS (red) in 2016-17 (Pienter 3-study) in the national sample (NS). Age groups in years, except in the three youngest age groups of 0-7 months, 8-13 months and 14-23 months of age. mo = months. [20]

When focusing at (the surrogate for) individual protection measured by the serum bactericidal antibody (SBA) assay, a much smaller proportion of toddlers in Pienter 3 had SBA titers above the level of protection (seroprevalence 59% among 14-23-month-olds) compared to 90% in Pienter 2 (Figure 5). It is unknown why the seroprevalence at 14 months was lower in Pienter 3 than in Pienter 2 as the same vaccine has been used in these cohorts (NeisVac-C).

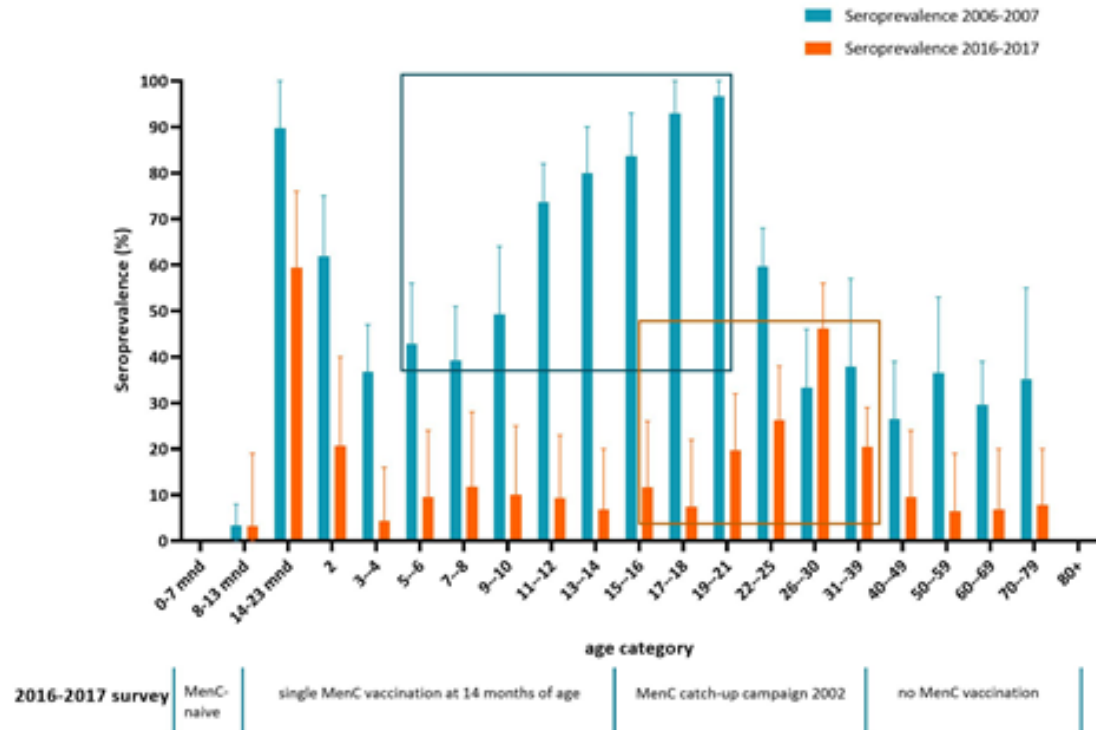*Figure 5 Seroprevalence of meningococcal C (MenC) bactericidal antibodies, determined by rSBA assay, in 2006-07 and 2016-17. Below the figure, the meningococcal vaccination schedules as received by the age groups at the moment of the 2016-17 serosurvey are indicated. [20]*

Data from the second round of a recent serosurvey (Pienter-corona or PICO study [21]; individuals aged three years and older, but low numbers at young age), sampled in June/July 2020 include 1782 self-collected fingerstick blood samples that were (also) analysed for MenACWY-PS IgG concentrations. Compared to the serosurvey in 2016-17, the MenW PS GMCs in PICO were much higher in teenagers that were eligible for MenACWY vaccination during the mass campaign that started in 2018. However, the majority of children and adults in the PICO-study did not have MenW PS IgG antibodies, reflecting the individual vulnerability in unvaccinated cohorts [20].

Together, the serological surveys show that MenACWY vaccination at 14 months and 14 years elicit good immune responses, that the proportion that has IgG levels above the cut-off for protection is higher among adolescents than among toddlers, and slightly lower when vaccinated at 14 compared to 18 years of age. The results are suggestive of waning of immunity, which may occur faster after the infants-dose than the adolescents dose; among the cohort that was vaccinated at age 17-18 years, after 10 years, about half of them had IgG levels above the cut-off for protection. Whether the immune response resulting from the 14-years-dose is sufficient and widespread enough to provide complete herd immunity so that the 14-months-dose could be omitted, cannot be concluded based just on these data.

Could the second dose be given earlier, when that would be desirable for programmatic reasons?
The MenACWY vaccine induces a robust antibody response with bactericidal activity but the level and duration of protection differs according to the age of the immunisation. A comparison was made between adolescents that were vaccinated with MenC at the age of 10, 12 and 15 years. The majority of participants seroconverted and maintained bactericidal titers over 128 (indicative cut-off for protection on the longer term) after 1 year of a single vaccination. The bactericidal responses were higher in adolescents vaccinated at 12 or 15 years of age compared with those vaccinated at 10 years of age and there was a non-significant trend of higher titers at 15 than 12 years [18, 19]. Three years after vaccination, the 15-year-olds showed the highest antibody titers that were indicative for slower waning of immunity, although it cannot be excluded that exposure rather than intrinsic biological age effects explain the age differences. In a study providing a single MenACWY vaccination in, among others, adolescents, 94-97% showed protective titres after 5 years [22]. Overall, these data indicate that when vaccination is given at a slightly younger age this likely will be at the expense of somewhat reduced immunity and possible decreased herd protection. The vaccination would therefore not be given before 12 years, but 14 years seems better as the duration of protection seems shorter for younger ages, and it is desirable that those with highest carriage rates i.e., at around 18 years, and students that may show more risk behaviour for respiratory infections, should still be protected. Vaccination should not be much delayed as carriage rates are already substantial and increasing from 15 years old [13-15].

Evaluation of MenB vaccination against IMD-B
Besides the described conjugate vaccines, two recombinant protein meningococcal B vaccines (4CmenB - Bexsero, and MenB-FHbp - Trumenba) are available and licensed for use in The Netherlands, which can be used from 2 months old (Bexsero) or 10 years old (Trumenba). These protein vaccines are effective in prevention of IMD-B but do not affect carriage [23]. As these protein antigens can also be expressed by non-MenB strains, MenB vaccines may also partially protect against IMD caused by other serogroups, depending on the strain coverage. For The Netherlands, it was predicted based on genetic analysis of Dutch IMD isolates that 4CmenB may prevent up to 73% of all cases and 58% of children aged 0-4 years [11]. A pentavalent vaccine combining the protein-based MenB and polysaccharide conjugate MenACWY components targeted at protection against IMD-A, B, C, W and Y is being developed (phase I) but not yet available [24].

MenB vaccination is not part of this evaluation of the current vaccination schedule; the Health Council is planning to evaluate the inclusion of MenB vaccination in the NIP in 2022.

3.8.6   *Summary and conclusions; suggestions for the request for advice from the Health Council*
The current schedule of MenACWY vaccination at 14 months and 14 years of age effectively protects the targeted age groups and provides increasing indirect protection to non-targeted age groups. If vaccination coverage remains stably high and complete indirect protection will be

established, the Health Council may want to consider discontinuing the 14-months dose.

The timing of the vaccinations seems appropriate for reaching the aims of the programme. If, for programmatic reasons, it would be desirable to administer the now second MenACWY vaccine dose earlier, it should be noted that such a change might go at the expense of immunity levels, duration of protection, and possibly, indirect protection.

Serogroup B has now become the most common serogroup causing IMD in The Netherlands. About two-thirds of those cases may be prevented by specific and separate vaccination. Assessment of potential inclusion of vaccination against meningococcal disease caused by serogroup B already is on the agenda of the Health Council for 2022.

3.8.7 References

1   Knol, M.J., et al., *Implementation of MenACWY vaccination because of ongoing increase in serogroup W invasive meningococcal disease, the Netherlands, 2018.* Euro Surveill, 2018. **23**(16).

2.   Zorginstituut Nederland. *Farmacotherapeutisch kompas: Meningokokkenvaccin type A, C, W135, Y.* 2021; Available from: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/m/meningokokkenvaccin_type_a__c__w135__y.

3.   McMillan, M., et al., *Effectiveness of meningococcal vaccines at reducing invasive meningococcal disease and pharyngeal Neisseria meningitidis carriage: A systematic review and meta-analysis.* Clin Infect Dis, 2020.

4.   Cohn, A.C., et al., *Effectiveness and Duration of Protection of One Dose of a Meningococcal Conjugate Vaccine.* Pediatrics, 2017. **139**(2).

5.   Ohm, M., et al., *Vaccine impact and effectiveness of meningococcal serogroup ACWY conjugate vaccine implementation in the Netherlands: a nationwide surveillance study.* Clin Infect Dis, 2021.

6.   de Oliveira Bressane Lima, P., et al., *MenACWY vaccination campaign for adolescents in the Netherlands: Uptake and its determinants.* Vaccine, 2020. **38**(34): p. 5516-5524.

7.   Health Council of the Netherlands, *Vaccinatie tegen meningokokken.* 2018.

8.   Middeldorp, M., et al., *Short term impact of the COVID-19 pandemic on incidence of vaccine preventable diseases and participation in routine infant vaccinations in the Netherlands in the period March-September 2020.* Vaccine, 2021. **39**(7): p. 1039-1043.

9.   Meerveld-Eggink, A., et al., *Impaired antibody response to conjugated meningococcal serogroup C vaccine in asplenic patients.* Eur J Clin Microbiol Infect Dis, 2011. **30**(5): p. 611-8.

10.   Bijlsma, M.W., et al., *A decade of herd protection after introduction of meningococcal serogroup C conjugate vaccination.* Clin Infect Dis, 2014. **59**(9): p. 1216-21.

11. Freudenburg-de Graaf, W., M.J. Knol, and A. van der Ende, *Predicted coverage by 4CMenB vaccine against invasive meningococcal disease cases in the Netherlands.* Vaccine, 2020. **38**(49): p. 7850-7857.

12. Ladhani, S.N., et al., *Vaccination of Infants with Meningococcal Group B Vaccine (4CMenB) in England.* N Engl J Med, 2020. **382**(4): p. 309-317.

13. Marshall, H.S., et al., *Meningococcal B Vaccine and Meningococcal Carriage in Adolescents in Australia.* N Engl J Med, 2020. **382**(4): p. 318-327.

14. MacLennan, J.M., et al., *Meningococcal carriage in periods of high and low invasive meningococcal disease incidence in the UK: comparison of UKMenCar1-4 cross-sectional survey results.* Lancet Infect Dis, 2021. **21**(5): p. 677-687.

15. Watle, S.V., et al., *Meningococcal carriage in Norwegian teenagers: strain characterisation and assessment of risk factors.* Epidemiol Infect, 2020. **148**: p. e80.

16. Martinon-Torres, F., et al., *Evolving strategies for meningococcal vaccination in Europe: Overview and key determinants for current and future considerations.* Pathog Glob Health, 2021: p. 1-14.

17. European Centre for Disease Prevention and Control. *Surveillance Atlas of Infectious Diseases*. 2021; Available from: https://atlas.ecdc.europa.eu/public/index.aspx.

18. van Ravenhorst, M.B., et al., *Meningococcal serogroup C immunogenicity, antibody persistence and memory B-cells induced by the monovalent meningococcal serogroup C versus quadrivalent meningococcal serogroup ACWY conjugate booster vaccine: A randomized controlled trial.* Vaccine, 2017. **35**(36): p. 4745-4752.

19. van Ravenhorst, M.B., et al., *Adolescent meningococcal serogroup A, W and Y immune responses following immunization with quadrivalent meningococcal A, C, W and Y conjugate vaccine: Optimal age for vaccination.* Vaccine, 2017. **35**(36): p. 4753-4760.

20. Ohm, M., et al., *Seroprevalence of meningococcal ACWY antibodies across the population in the Netherlands: two consecutive surveys in 2016/17 and 2020* Vaccine, 2021.

21. Vos, E.R.A., et al., *Nationwide seroprevalence of SARS-CoV-2 and identification of risk factors in the general population of the Netherlands during the first epidemic wave.* J Epidemiol Community Health, 2020.

22. Ohm, M., et al., *Different Long-Term Duration of Seroprotection against Neisseria meningitidis in Adolescents and Middle-Aged Adults after a Single Meningococcal ACWY Conjugate Vaccination in The Netherlands.* Vaccines (Basel), 2020. **8**(4).

23. McMillan, M., et al., *Impact of meningococcal B (4CMenB) vaccine on pharyngeal Neisseria meningitidis carriage density and persistence in adolescents.* Clin Infect Dis, 2020.

24. U. S. National Library of Medicine. *ClinicalTrials.gov: A Study on the Safety, Effectiveness and Immune Response of Meningococcal Combined ABCWY Vaccine in Healthy Adolescents and Adults*. 2021; Available from: https://clinicaltrials.gov/ct2/show/NCT04886154

3.9 Mumps

3.9.1 History of vaccination against mumps
Vaccination against mumps has been part of the NIP in The Netherlands
from 1987, as MMR for children 14 months and 9 years of age.

3.9.2 Goal of vaccination against mumps
To prevent complications (orchitis, meningitis, encephalitis) and residual
problems (deafness, sterility in boys/men) of mumps.

3.9.3 Epidemiology of mumps in The Netherlands
Before the introduction of mass vaccination all children were infected
mumps virus, mostly at 5-9 years of age. Complications included aseptic
meningitis (1-10%) and encephalitis (0,1%); for these conditions yearly
300-800 children were hospitalized. In atypical cases of mumps post
puberty about 15-30% of men developed orchitis, usually one-sided, in
which cases sterility was rare; among women about 5% developed an
inflammation of the ovaries, with no negative consequences for fertility
usually. A rare complication of meningo-encephalitis was deafness.[1]

Routine vaccination against mumps exerted excellent control over the
disease [2]. In The Netherlands, the mortality of mumps in the pre-
vaccination era declined from 30 cases in the 1950s, to 17 and 16 in the
1960s and 1970s respectively. In the 1980s 7 deaths were reported, of
which the last in 1988. Hospitalization data are available since 1980. In
the period 1980-1987, 300 to 400 cases were hospitalized annually,
with higher numbers in 1980 and 1983 when 702 and 782 patients,
respectively, were admitted. [3] Following the introduction of mumps
vaccination in the NIP in 1987, mortality due to mumps became rare,
with only three death reported between 1990 and 2020. In the first five
years after introduction of vaccination the number of hospitalizations
decreased to around 10 cases per year, and was between 1 and 6 cases
per year until 2007. Between August 2007 and May 2009a major
reemergence of mumps in The Netherlands occurred during August
2007–May 2009, when a large outbreak of genotype D mumps occurred
that affected mainly unvaccinated persons with a religious objection; 43
patients were hospitalized. From 2009 to 2015, the latest year for which
data are available, 5 to 15 hospitalizations were reported annually.

Notification data are available since 1976 and show a large decline in
the incidence of mumps in The Netherlands after introduction of the
vaccine in the NIP in 1987 (Figure 1). However, from late 2009 until
2012, a countrywide epidemic with over 1500 reported cases occurred
that especially affected (vaccinated) student populations [4]. Since
2012, the number of reported mumps cases among students has
declined in The Netherlands. In 2019, 131 cases of mumps were
reported, and although this reflects a relative low incidence (0.8 per
100,000), it was two-fold higher than that of the previous year. In the
first quarter of 2020 the number of reported cases was again higher
than in Q1 of 2019 (61 vs 30). The number of cases declined abruptly in
early April 2020 as a result of measures introduced in response to
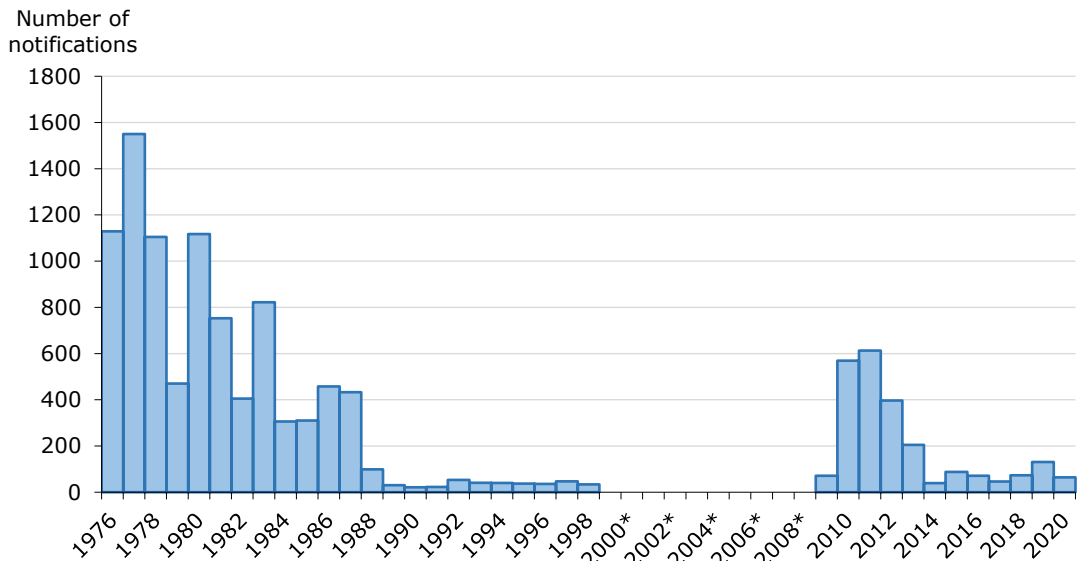COVID-19.

Number of
notifications

Figure 1 Number of notified mumps cases in the period 1976-2020
* From 2000 to 2008 mumps was not notifiable

3.9.4   *Assessment of the vaccination against the six criteria, issues identified*
1. Is the protection adequate for all those intended to be protected?
Routine vaccination against mumps has been shown to be very
efficacious, since the number of reported mumps cases and
hospitalizations were drastically reduced after implementation of this
vaccine in the NIP. In the past decade, however, an increase of mumps
cases is observed. In contrast to the pre-vaccination era, where mumps
cases were mainly reported amongst 5-9 years old children, nowadays
mumps cases are often seen in vaccinated adolescents and young
adults. Due to the changing epidemiology, in which mumps occur at a
later age, orchitis now is the complication most often reported. The full
implications of the change are not yet clear.

Issues related to this criterion:
   i.   The benefits of mumps vaccination are manifest by a reduction of
          cases and complications in the original target group of young
          children (e.g. meningitis, permanent deafness, pancreatitis,
          encephalitis). However, an increase of relatively mild cases is
          observed among vaccinated adolescent and young adults. Most
          notably, an increase of orchitis cases is observed among
          previously vaccinated adolescent boys and young men. How to
          weigh this relatively recent development against the success of
          the vaccination programme as set up to protect young children?

2. Is the applied vaccination strategy optimal?
The vaccination schedule comprises a first dose at 14 month of age,
followed by a second (booster) dose at 9 years of age. Most children
(approximately 97%) respond to a first dose of vaccination, and
generate a sustained antibody response. Some waning of mumps-
specific antibodies is observed, but mumps cases are rare among
vaccinated children before the second dose is administered at nine years
of age are rare. The second dose boosts the antibody levels and it also
provides a second chance to build up immunity for children that did not

respond at the first dose. After the second dose, mumps-specific antibodies again wane slightly over time. It is not exactly clear how the waning of antibodies is related to the increase of mumps outbreaks amongst (vaccinated) adolescent and young adults. During such mumps outbreaks, a third vaccination targeting young adults at risk might be an effective measure for control, if the intervention is implemented on time and vaccination coverage is high. Overall, the current general vaccination of children supplemented with targeted vaccination during outbreaks is considered both effective and efficient. If further protection of adolescents and young adolescents is deemed to be within the scope of the NIP (issues i and iii), the strategy will have to be adjusted accordingly.

3. Does the programme include too much?
No. The first dose at 14 month of age protect the majority of children, and immunity is further boosted at 9 years of age for long-term protection. Also, first-dose non-responders often do show an immune response after their second dose at 9 years of age. Therefore, the two-dose vaccination scheme can be considered both effective and efficient.

4. Does the programme include too little?
The current programme protects young children against severe mumps and its complications. Adolescents and young adults are also protected, but this protection is limited: mostly mild cases of mumps occur among adolescents and young adults, commonly under conditions of crowding and intense contact, and an increase of cases with orchitis is observed. Outbreaks can be contained by targeted vaccination. If it is deemed necessary to extend the protection of adolescents and young adults further action may be required. This issue will be discussed in relation to criterion 1.

5. Is the timing of immunisations using combination vaccines optimal or at least acceptable?
The current timing of mumps vaccination is acceptable. The first dose at 14 month of age protects children and the booster vaccination at 9 years of age extents protection most likely for another 10 years, at least until adolescence. A delay of the second dose to 12-14 years of age might be considered, in order to extent protection in young adults, but as yet no scientific data is available to support or reject this. Moreover, this also depends on the judgement whether preventing mumps in young adults should be considered a goal of the NIP, since symptoms are generally mild.

Issue related to this criterion:
  ii.   Most children develop an effective immune response to their first dose of mumps vaccine. A small proportion of vaccinated children do not respond to their first dose of mumps vaccine; however, most of them mount an effective immune response to the second dose. After the first dose, immunity against mumps infection wanes over time, but rarely so that it leads to reinfection before the age of the booster dose at nine years of age. The second dose boosts immunity effectively, leading to protective immunity throughout adolescence. Could postponing the second dose of

mumps vaccine to the age of 12-14 years lengthen the period of protective immunity after immunisation?

6. Are there important drawbacks of the NIP? For the population as a whole? For those who opt out? How are these drawbacks to be weighed against the advantages of the programme and its components?

For the general population: As a result of the introduction of mumps vaccination in 1987, the average age of reported mumps cases shifted from 5-9 years to 18-25 years old and most mumps outbreaks are now reported amongst vaccinated students/young adults, that are protected against mumps at least partly and will present with relatively mild symptoms if they might develop mumps. Outbreaks can be contained by targeted vaccination of students/young adults. The benefits of the national mumps vaccination programme (i.e. hardly any mumps cases in children with more severe and long-term complications) outweighs the drawbacks of the shift in age of reported mumps outbreaks.
In areas with low vaccine coverage, mumps outbreaks may affect unvaccinated children and adults up to 40 years of age, that have not been infected with mumps before and who may present with more severe disease and complications.

Issues related to this criterion:
  iii.   Mumps outbreaks are reported primarily among students/adolescents and are linked to crowding and intense contact. Should preventing such outbreaks have consequences for the NIP or do the limited disease burden that they pose and the fact that they can be contained by targeted vaccination relatively easily lead to the opposite conclusion? (covering roughly the same topic as the first issue)
  iv.   Mumps vaccination coverage is low in some socio-geographically clustered protestant orthodox reformed communities. Since the implementation of mass vaccination against mumps, cases amongst unvaccinated individuals occur relatively often at an older age, with orchitis as its main complication. Does the general benefit for the Dutch population overall outweigh a possibly negative effect in these communities?

3.9.5   *Exploration of the issues against the available knowledge*
  How to weigh the increased incidence of mumps among vaccinated adolescents and young adults?
  i.   The benefits of mumps vaccination are manifest by a reduction of cases and complications in the original target group of young children. However, an increase of relatively mild cases is observed among vaccinated adolescent and young adults, probably due to waning immunity. Most notably, an increase of orchitis cases is observed among previously vaccinated adolescent boys and young men. How to weigh this relatively recent development against the success of the vaccination programme as set up to protect young children?
  iii.   Mumps outbreaks are reported primarily among students/adolescents and are linked to crowding and intense contact. Should preventing such outbreaks have consequences for the NIP or do the limited disease burden that they pose and

the fact that they can be contained by targeted vaccination relatively easily lead to the opposite conclusion?

Vaccine effectivity
The first live attenuated mumps virus vaccines for routine use were developed in the 1950s in the former Soviet Union and in the 1960s in the United States[5]. In most developed countries, mumps vaccination has been implemented as part of a trivalent vaccine with measles and rubella viruses (i.e., MMR). Mumps vaccine is also available as tetravalent vaccine ProQuad and Priorix-Tetra with measles, rubella and varicella viruses (i.e., MMRV). The vaccine containing the Jeryl Lynn mumps virus strain, was licensed in 1967, and is the only mumps vaccine approved for use in the United States and most European countries, including The Netherlands; it is used widely throughout the world [5]. Nowadays two MMR vaccine products, that are licensed in The Netherlands, are available, i.e. MMR-VAX-PRO and Priorix (https://www.geneesmiddeleninformatiebank.nl/nl/). Both live attenuated vaccines are supplied as lyophilized powders and are administered intramuscularly or subcutaneously following reconstitution with sterile water. MMR vaccine administered by the intramuscular route has shown to result in comparable antibody response rates with slightly lower rates of injection-site erythema and swelling than subcutaneous administration [6]. Both vaccines contain sorbitol and may contain trace amounts of neomycin. Despite the use of chicken embryo as cell substrate for mumps virus, few serious allergic reactions have been attributed to egg protein [7]. The low rate of vaccine-associated adverse events reported with these products attests to their excellent safety profile [8].

For optimal efficacy, mumps vaccination is administered twice. According to the marketing authorization holder of the MMR vaccine, a first dose of the vaccine induces a primary immune response and is indicated for individuals from 12 months of age. Studies have shown that a first vaccination before 6 months of age is less effective, since the immune system of young infants is too immature for a live-attenuated vaccine.[5] A second dose of the vaccine boosts the mumps-specific antibody levels. The age of this second dose varies between different countries, ranging from 4 to 12 years old. Following the Dutch National Immunisation Program, children receive two doses of mumps vaccine (as component of MMR); the first at 14 months, and the second at 9 years of age.

Vaccination protects against complications of mumps. A Dutch study into viral shedding and severity of disease included 1100 mumps patients tested between 2007 and 2014, of whom around 600 were twice vaccinated and 200 unvaccinated. Shedding of mumps virus in urine (i.e., viruria) is an indication of systemic mumps diseases, in contrast to shedding in saliva only. The study found that viral loads in saliva did not differ between vaccinated and unvaccinated patients, but that viral shedding in urine occurred less in twice vaccinated patients. Bilateral parotitis and orchitis were less often reported in patients who had received 2 MMR doses than in unvaccinated patients. Furthermore, the prevalence of bilateral parotitis and orchitis was higher among twice

MMR vaccinated patients with viruria than among twice MMR vaccinated patients without viruria. [9]

The effectiveness of mumps vaccination in the Dutch population was calculated most recently during an outbreak amongst students in 2009-2012 [4]. This study showed a reduced risk for orchitis in persons who had been vaccinated with 2-doses (vaccine effectiveness (VE) 74%, 95%CI 57%-85%). The risk for hospitalization was also reduced: the estimated VE for preventing hospitalization was 82% (95%CI 53%-93%). Orchitis with mumps usually is one-sided and does not lead to sterility, whether among persons previously vaccinated or not. Formal studies comparing the risk of sterility among persons previously vaccinated or not, however, are not known.

Waning immunity
Since no correlates of protection have been determined for mumps, it is difficult to determine who is at risk of infection and who is not. Recently, a surrogate cut-off for seroprotection against mumps virus infection was determined by evaluating antibody levels in preoutbreak serum from persons with versus without serological evidence of mumps. The most appropriate IgG antibody cut-off level to discriminate persons who were susceptible to mumps virus infection from those protected against mumps virus infection was determined to be 102 RIVM units (RU)/mL [10]. Previously an IgG antibody cut-off level of 45RU/mL was used as a criterion for seroprevalence of mumps antibodies [11].

Data from two Dutch cohorts showed that mumps-specific IgG concentrations just before routine administration of MMR2 at nine years of age were lower than 9-16 years after administration of MMR2 at the age of 18–25 years (geometric mean concentrations [GMC] of 120 RU/mL vs 185 RU/mL, respectively). Apparently, administration of MMR2 resulted in an increase of IgG concentrations against mumps virus infection, which remained elevated at the age of 18–25 years. The mumps seroprotection rate (i.e., percentage of individuals above the cut-off (102 RU/mL) for presumed seroprotection) was also considerably lower before receipt of MMR2 (50%) compared with receipt of MMR3 (81%) [12]. This emphasizes the importance of routine MMR2 for children and young adults for protection against mumps.

Mumps immunity wanes over time and people can become susceptible to mumps infection approximately >10 years after the second dose of vaccination. It has been reported that up to 26% of persons fully vaccinated for mumps do no longer have detectable mumps-specific antibodies 15 years after receiving their last vaccination [5]. No clear correlates of protection are defined, so it is not feasible to identify persons at risk.

Other immunological factors
Other immunological factors could contribute to the increased incidence of mumps among adolescents and young adults. Next to waning of antibodies, the cellular responses induced by mumps vaccination seem to be suboptimal in the long run. Mumps-vaccination induces low numbers of memory B cells, compared to measles- and rubella-specific memory B cells after MMR vaccination. And although mumps-specific

cellular proliferation has been detected 21 years after vaccination, frequencies of vaccine-induced mumps-specific T cells are lower compared to infection-induced responses. Moreover, these vaccine-induced T cells also show less polyfunctionality, indicating suboptimal immunity to mumps [13].

Still another could be an antigenic mismatch of the circulating outbreak strain and the vaccine strain. Current mumps outbreak strains are of Genotype G, whereas the mumps-vaccine is based on the Genotype A strain [14]. Several studies indicate that antigenic differences between vaccine and circulating mumps virus strains (mismatch) may affect the antibody response. But also T cell immunity may be reduced as a result of this antigenic mismatch. In silico prediction models show for both T-helper cells [15] and cytotoxic T cells [16] a potential reduced response due to antigenic differences between vaccine and circulating mumps virus strains. To what extent antigenic a mismatch between circulating and vaccine strains contributes to the current outbreaks remains unknown.[10, 12]

Several immunological factors contribute to a decrease in mumps vaccine effectiveness, and experts have called for the development of a new vaccine based on a strain that is safe and more immunogenic than the Jeryl Lynn strain. [17]

Seroprevalence studies
In 2016/17, the third Pienter-study was conducted primarily aimed to assess the population immunity against vaccine-preventable diseases in The Netherlands.[18] In the national cohort, overall mumps weighted seroprevalence was 92.4% (95% CI 91.5-93.3) based on a cut-off of 45 RIVM units (RU)/mL for seropositivity and estimates did not differ significantly between sexes (men: 92.1% and women: 92.8%). Figure 2 shows mumps antibody geometric mean concentration (GMC) and the weighted seroprevalence by age groups for the 45 RU/mL cut-off and the more conservative cut-off of 102 RU/mL by age, that is more suggestive of a seroprotective level as discussed previously. Maternal antibodies decrease in the first months of life and after the first dose of MMR at 14 months seroprevalence increased steeply to over 90% at the age of 2 years and decreased to around 80% before 9 years. The GMC increases from below 45 RU/mL to around 140 RU/mL at the age of 2 years and waned to around 100 RU/mL before 9 years of age, the current eligible age for the second MMR shot. Likewise, after administration of the second dose of MMR, GMC increases sharply to between 200 and 250 RU/mL at 9 years of age and wanes to a level of around 150 RU/mL in participants in the vaccinated cohorts aged 20 to 30 years old. Waning after the second dose of MMR in the vaccinated cohorts is also reflected in the seroprevalence for both cut-offs, which is highest at 10 years of age and lowest in 30-32 year olds (except for seroprevalence at 45 RU/mL cut-off in the 21-23 year olds). GMC and seroprevalence are higher in pre-vaccine age cohorts, being in their early thirties and older at the time of the current Pienter 3 study.
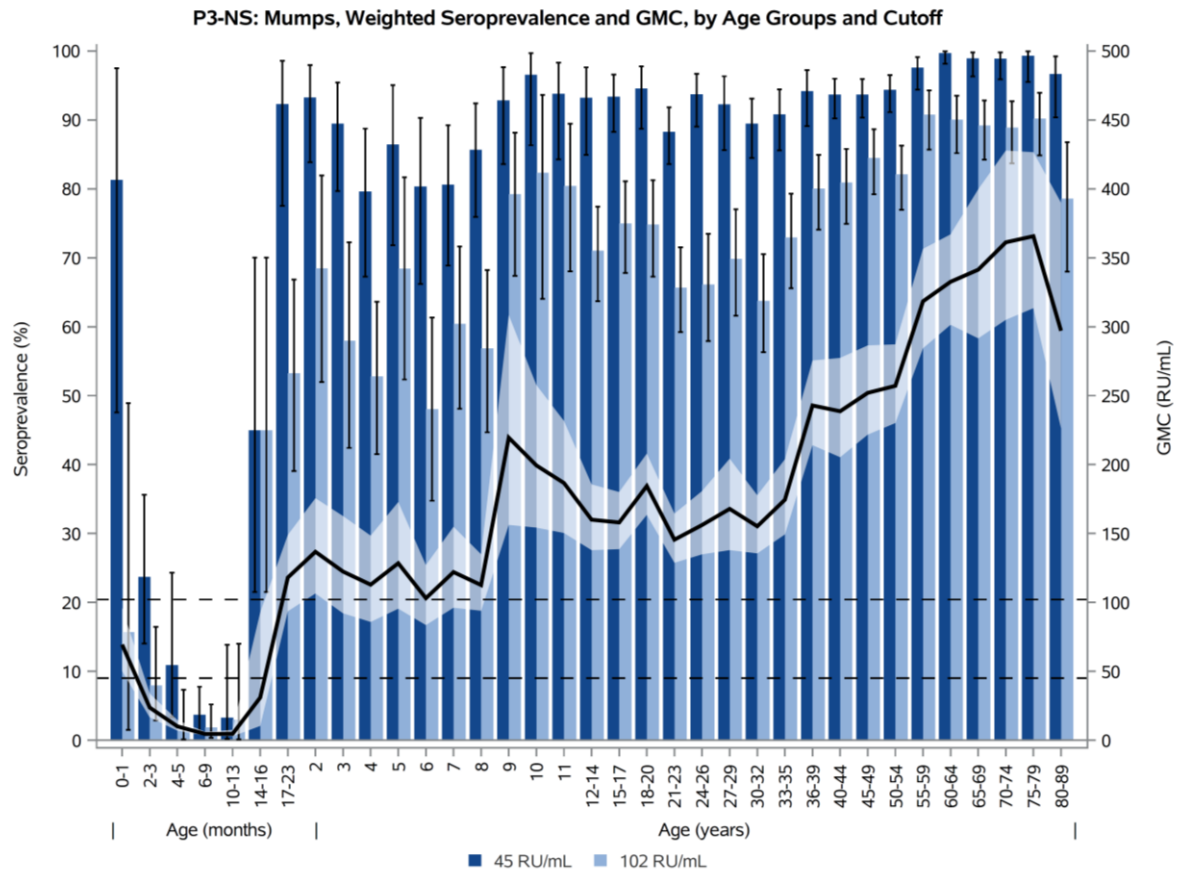
Figure 2 Mumps, weighted seroprevalence (bars) and geometric mean concentration (GMC, line) both with 95% confidence intervals/envelop, by age group (months and years) in the general Dutch population, from the Pienter 3 study (2016-2017). The dashed lines indicate the cut-offs of 45 and 102 RU/mL.

Studies among students/adolescents and young adults

Several studies have been conducted around the outbreak among students in The Netherlands in 2009-2012. A survey among almost 1,000 members of student associations invited to a large party found an attack rate of self-reported mumps of 13%. Attending the party, being unvaccinated and living with more than 15 housemates were independently associated with mumps.[19] Another retrospective study around an outbreak at a youth club party yielded an attack rate of 22% and found smoking and older age (>20 years) as risk factors.[20] A serological study with paired pre- and post-outbreak samples from students indicated an attack rate for symptomatic mumps virus infection of 2.0%, and an overall attack rate including asymptomatic infections of 5.8%.[21] Circulation of mumps virus among housemates was an independent risk factor. A prospective cohort study including 99 contacts of 10 mumps cases found an attack rate of self-reported mumps of 4.0%.[22] These data highlight crowding and intense contact as factors contributing to outbreaks in vaccinated populations, which was also observed in other countries.[23]

Among vaccinated people, the majority of infections (63-80%) is asymptomatic.[21, 24, 25] If symptoms do occur, they usually are milder than in unvaccinated individuals. Aseptic meningitis and

encephalitis are rare. In outbreaks in the United States, Poland and The Netherlands 4-7% of men vaccinated twice developed orchitis (compared to 15-30% among post puberty mumps cases among men in the pre vaccination era).

A third dose of mumps-vaccination (MMR-3) was reported to be efficient in boosting the mumps-specific antibody response in young adults, and can therefore be used as a measure to protect young adults and prevent further circulation of the virus during an outbreak.[10, 12] Prerequisites are, however, that the intervention is implemented on time and vaccination coverage is high.

Could the second dose of mumps vaccine better be postponed?

ii.   Most children develop an effective immune response to their first dose of mumps vaccine. A small proportion of vaccinated children do not respond to their first dose of mumps vaccine; however, most of them mount an effective immune response to the second dose. After the first dose, immunity against mumps infection wanes over time, but rarely so that it leads to reinfection before the age of the booster dose at nine years of age. The second dose boosts immunity effectively, leading to protective immunity throughout adolescence. Could postponing the second dose of mumps vaccine to the age of 12-14 years lengthen the period of protective immunity after immunisation?

The vaccination schedule of the MMR vaccines differs between countries. Especially the age at which the second dose of MMR vaccine is administered differs, ranging from 15-23 months to 13 years of age in Europe.[26] A review of literature available on PubMed published between 2010 and 2021 identified a limited number of outbreaks that occurred mainly among twice vaccinated children aged 13-18 years (references available upon request), while the vast majority of reported outbreaks occurred among twice vaccinated young adults aged 18-25 years. Outbreaks that were reported (mainly) among children aged 13-18 years occurred in countries in which the second dose of MMR was administered at 6 years of age or younger and were often associated with a period of close contact.

The second dose is given at 9 years of age in The Netherlands, which is late compared to most other countries in Europe. Only a few countries administer the second dose of MMR at 11-12 years of age (Norway, Hungary, Iceland, Bulgaria) or even 13 years of age (Estonia). There is limited data to assess the potential effect of later administration of the second dose. Postponing the second dose with 2 or 3 years is not likely to prevent outbreaks among students, as Norway, where MMR uptake is high, reported a mumps outbreak among mainly vaccinated students in 2015-2016 related to a student festival.[27] There is no scientific basis for postponement of the second dose of MMR in order to improve the protection against mumps.

Mumps in communities with low vaccination coverage

iv.   Mumps vaccination coverage is low in some socio-geographically clustered orthodox protestant communities. Since the implementation of mass vaccination against mumps, cases

amongst unvaccinated individuals occur relatively often post puberty, with orchitis as its main complication . Does the general benefit for the Dutch population overall outweigh a possibly negative effect in these communities?

In 2007-2009 an outbreak of mumps occurred in orthodox protestant communities with low vaccination coverage. The median age of the patients was 13-15 years, which is lower than the median age during the epidemic period 2010-2012 (23 years), and the period 2013-2020 when the median age of reported cases increased to 26 years.[28] After 2009 further outbreaks of mumps in the so-called bible belt have not been reported. However, Pienter data show higher levels of susceptibility in participants in municipalities with low vaccination coverage that are born after the last outbreak of mumps in 2008. Increasing numbers of susceptibles could result in future mumps outbreaks in these communities; the mean age of infection is expected to increase with an increasing interval until the next outbreak.

3.9.6   *Suggestions for the request for advice from the Health Council*
The main topic for advice from the Health Council is how the increase of cases of mumps among students/adolescents and young adults should we weighted, whether or not the protection of these groups should be considered to be within the scope of the NIP and what specific measures are deemed appropriate. In relation to that topic, a call for the development of a new mumps vaccine could be made.

3.9.7   *References*

1.   Hviid, A., S. Rubin, and K. Muhlemann, *Mumps.* Lancet, 2008. **371**(9616): p. 932-44.
2.   Plotkin, S.O., Walter; Offit, Paul; Edwards, Kathryn M., *Plotkin's Vaccines*. 2017: Elsevier. 1720.
3.   Hof van den, S., et al., *The effects of vaccination, the incidence of the target diseases*. 1998, National Institute for Public Health and the Environment (RIVM).
4.   Sane, J., et al., *Epidemic of mumps among vaccinated persons, The Netherlands, 2009-2012.* Emerg Infect Dis, 2014. **20**(4): p. 643-8.
5.   Rubin, S.A., *Mumps Vaccines*, in *Plotkin's Vaccines*. 2018, Elsevier: Philadelphia, PA. p. 663-688.
6.   Gillet, Y., et al., *Immunogenicity and safety of concomitant administration of a measles, mumps and rubella vaccine (M-M-RvaxPro) and a varicella vaccine (VARIVAX) by intramuscular or subcutaneous routes at separate injection sites: a randomised clinical trial.* BMC Med, 2009. **7**: p. 16.
7.   Patja, A., et al., *Allergic reactions to measles-mumps-rubella vaccination.* Pediatrics, 2001. **107**(2): p. E27.
8.   Lievano, F., et al., *Measles, mumps, and rubella virus vaccine (M-M-RII): a review of 32 years of clinical and postmarketing experience.* Vaccine, 2012. **30**(48): p. 6918-26.
9.   Gouma, S., et al., *Severity of mumps disease is related to MMR vaccination status and viral shedding.* Vaccine, 2016. **34**(16): p. 1868-73.

10. Kaaijk, P., et al., *A Third Dose of Measles-Mumps-Rubella Vaccine to Improve Immunity Against Mumps in Young Adults.* J Infect Dis, 2019.

11. Andrews, N., et al., *The European Sero-Epidemiology Network: standardizing the enzyme immunoassay results for measles, mumps and rubella.* Epidemiol Infect, 2000. **125**(1): p. 127-41.

12. Kaaijk, P., et al., *Dynamics of the Antibody Response After a Third Dose of Measles-Mumps-Rubella Vaccine Indicate a Slower Decline Compared With a Second Dose.* Open Forum Infect Dis, 2020. **7**(11): p. ofaa505.

13. de Wit, J., et al., *Mumps infection but not childhood vaccination induces persistent polyfunctional CD8(+) T-cell memory.* J Allergy Clin Immunol, 2018. **141**(5): p. 1908-1911 e12.

14. Gouma, S., et al., *Two major mumps genotype G variants dominated recent mumps outbreaks in the Netherlands (2009-2012).* J Gen Virol, 2014. **95**(Pt 5): p. 1074-1082.

15. Homan, E.J. and R.D. Bremel, *Are cases of mumps in vaccinated patients attributable to mismatches in both vaccine T-cell and B-cell epitopes?: An immunoinformatic analysis.* Hum Vaccin Immunother, 2014. **10**(2): p. 290-300.

16. Kaaijk, P., et al., *Genetic Analysis Reveals Differences in CD8(+) T Cell Epitope Regions That May Impact Cross-Reactivity of Vaccine-Induced T Cells against Wild-Type Mumps Viruses.* Vaccines (Basel), 2021. **9**(7).

17. Plotkin, S.A., *Commentary: Mumps vaccines: do we need a new one?* Pediatr Infect Dis J, 2013. **32**(4): p. 381-2.

18. Verberk, J.D.M., et al., *Third national biobank for population-based seroprevalence studies in the Netherlands, including the Caribbean Netherlands.* BMC Infect Dis, 2019. **19**(1): p. 470.

19. Greenland, K., et al., *Mumps outbreak among vaccinated university students associated with a large party, the Netherlands, 2010.* Vaccine, 2012. **30**(31): p. 4676-80.

20. Ladbury, G., et al., *Smoking and older age associated with mumps in an outbreak in a group of highly-vaccinated individuals attending a youth club party, the Netherlands, 2012.* Euro Surveill, 2014. **19**(16): p. 20776.

21. Gouma, S., et al., *Mumps serum antibody levels before and after an outbreak to assess infection and immunity in vaccinated students.* Open Forum Infect Dis, 2014. **1**(3): p. ofu101.

22. Hahne, S., et al., *Mumps transmission in social networks: a cohort study.* BMC Infect Dis, 2017. **17**(1): p. 56.

23. Lam, E., J.B. Rosen, and J.R. Zucker, *Mumps: an Update on Outbreaks, Vaccine Efficacy, and Genomic Diversity.* Clin Microbiol Rev, 2020. **33**(2).

24. Cortese, M.M., et al., *Mumps antibody levels among students before a mumps outbreak: in search of a correlate of immunity.* J Infect Dis, 2011. **204**(9): p. 1413-22.

25. Dittrich, S., et al., *Assessment of serological evidence for mumps virus infection in vaccinated children.* Vaccine, 2011. **29**(49): p. 9271-5.

26. European Center for Disease Prevention and Control, E., *Vaccine Scheduler*.

27.   Veneti, L., et al., *Large outbreak of mumps virus genotype G among vaccinated students in Norway, 2015 to 2016.* Euro Surveill, 2018. **23**(38).

28.   Schurink-van 't Klooster, T. and H.E. de Melker, *The National Immunisation Programme in the Netherlands. Surveillance and developments in 2019-2020*. 2020, RIVM: Bilthoven.

3.10   Measles

3.10.1   *History of vaccination against measles*

In 1976, a stand-alone single-dose live-attenuated measles vaccine was introduced in the NIP for children at 14 months of age. In 1987 the stand alone vaccine was replaced by the MMR (measles-mumps-rubella) combination vaccine, which is since then given to children at the age of 14 months and at 9 years. The birth cohort 1983-1985 was offered a catch-up programme at the age of four years. Several measles vaccine types exist, most of them derived from an Edmondson isolate from 1954.[1]

3.10.2   *Goal of vaccination against measles*

The main goal of vaccination against measles is prevention of measles. This can be achieved by maintaining herd immunity in The Netherlands. A second goal is elimination of measles from the European region.

3.10.3   *Epidemiology of measles in The Netherlands*

Measles virus is one of the most contagious pathogens known, and mostly affected school-age children in the pre-vaccination era. In settings with good access to health care the most common complications of measles are otitis media (7-9%) and pneumonia (1-6%). Encephalitis is less common and occurs in about 1-4 per 1000-2000 reported cases, and the rare late onset complication subacute sclerosing panencephalitis (SSPE) occurs in 1 per 2500–10000 measles cases [1].

In The Netherlands, the incidence of measles declined rapidly after introduction of vaccination in 1976, but outbreaks are still observed in populations with low vaccination coverage. Years with over 1500 notified cases were observed in 1976-1977, 1988, 1999 and 2014. (figure 1). In the period 2015-2020 since the last outbreak, 139 cases of measles have been reported. In the last two outbreaks in 1999/2000 and 2013/2014 the estimated number of infections was approximately 37,000 and 31,000 respectively. Four patients died of measles during the last two nationwide outbreaks, and another three cases of SSPE occurred, resulting in an overall case fatality ratio of 0,01%. In the 2013/2014 outbreak, 94% of the 2700 reported cases was unvaccinated, and the median age of the patients was 10 years, 77% were between 4 and 17 years old, and 3% were below 14 months of age. Compared to the nationwide outbreaks, in the post outbreak period a higher proportion of cases occurs among vaccinated people (30%), and the median age is higher (range 17 to 32 years in the different years). Furthermore, the majority (68%) of cases since the last outbreak were imported or import related.
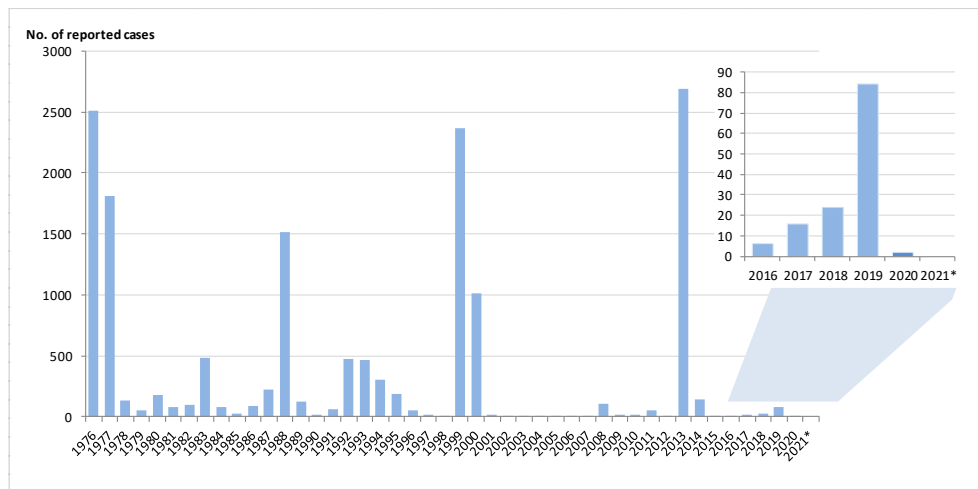
Figure 1 Annual reported measles cases since the introduction of measles in the Dutch vaccination programme.
* up to July

3.10.4 *Assessment of the vaccination against the six criteria, issues identified*
Criterion 1. Is the protection adequate for all those intended to be protected?
In general, the current measles vaccination schedule adequately protects all groups of children including preterm born infants and immunocompromised children. However, the presence of a specific region with a large socio-geographically clustered protestant orthodox reformed community ("bible belt") with a low vaccination coverage, in combination with a high basic reproduction number (R0) results in regular outbreaks. Specifically children who do not have maternal measles antibodies anymore (after 4-6 months of age),are too young to be vaccinated (<14 months of age) and live in this area are at increased risk of becoming infected with the measles virus.

Issue related to criterion 1
Children who are too young to be vaccinated and live in areas with low vaccination coverage, mainly in the bible belt, are at risk during an outbreak of measles.

Criterion 2. Is the applied vaccination strategy optimal?
Yes, most of the population is sufficiently protected.
Elimination is feasible but requires a vaccination coverage >95% due to the high contagiousness of the measles virus. The presence of clusters of unvaccinated individuals poses an increased risk for development of an outbreak after introduction of measles virus in The Netherlands. As long as the vaccination rate is <95% in clusters of unvaccinated people specific outbreak measures will be required.

Issue related to criterion 2
Clustering of unvaccinated individuals leads to increased risk of measles outbreaks after introduction of measles virus. Especially children in the orthodox protestant community are at risk.

Criterion 3. Does the programme include too much?
No. With current vaccines around 3% of the children that receive an MMR dose do not respond to the vaccine (primary vaccine failures). Most of these children (95%) do respond to a second MMR dose (>99% seroconvert after two doses if the first dose was administered after 12 months of age).

The second MMR dose is needed to increase number of responders and it results in a slower antibody waning in individuals that already responded after the first MMR dose. In conclusion, the two-dose programme is appropriate for vaccination against measles and does not include too much.

Criterion 4. Does the programme include too little?
No. Two vaccine doses is sufficient to protect the general population against measles.

Criterion 5. Is the timing of immunisations using combination vaccines optimal or at least acceptable?
Timing of current immunisation schedule for the MMR vaccine (doses at 14 months and 9 years of age) is acceptable for measles. Giving the first dose of MMR before 12 months of age results in reduced long term protection. Delaying the first dose will result in better protection after vaccination, but at the same time will result in a larger group of susceptible children, being all children who lack maternal antibodies and did not get vaccinated themselves yet. The incidence of measles can play a role in the decision of the MMR vaccination schedule; it can be anticipated that in countries with a relatively high incidence (as a result of a relatively low vaccination coverage), administration MMR1 will be recommended at an earlier age compared to countries with a lower incidence. In The Netherlands the incidence of measles is generally low and the timing of the first dose at 14 months can be considered optimal, except during an outbreak. The issue of protecting children too young to be vaccination in case of an outbreak is already defined under criterion 1 (issue ii).

The timing of the second dose could be optimized by giving it at an earlier age (2-4 years) than at 9 years. By reducing the time window between doses, children with primary vaccine failure will be protected at a younger age, and the number of susceptible children reduced. Giving the second MMR dose at a younger age might also improve vaccination uptake, as data from the past 5 years show that the uptake of the DTP booster at 4 years is 2-5% higher than the uptake of MMR2 at 9 years.

Issue related to criterion 5
Children with primary vaccine failure after the first dose of MMR are susceptible for a relative long period as the interval between the first and second MMR dose is almost 8 years.

Criterion 6. Are there important drawbacks of the NIP? For the population as a whole? For those who opt out? How are these drawbacks to be weighed against the advantages of the programme and its components?

The current measles vaccination programme protects the population as a whole including people that opt out for vaccination. However, in clusters of people who opt out the risk of outbreaks is higher (see issue i). Vaccination has greatly reduced circulation and exposure to measles virus, resulting in more time between outbreaks and an increase in the age of infection. Measles infection in adulthood is associated with a higher risk of complications compared to infection in children. As a consequence, when those opting out from vaccination do get measles, a higher age at infection increases the risk of complications.

Issue related to criterion 6
Persons opting out of the NIP have a high risk of measles infection in case of an outbreak, and a higher risk of complications when they get measles at adult age.

3.10.5   *Exploration of the issues against the available evidence*
Children who are too young to be vaccinated and live in areas with low vaccination coverage are at risk during an outbreak of measles
The elimination strategy that is effective for most of the population fails in communities with low vaccination coverage and needs to be supplemented there with an outbreak strategy. Children too young to be vaccinated can be protected by giving the first dose of MMR before the age of 14 months in case of an outbreak. However, the effectiveness of vaccination is influenced by the age at the first dose.

Several reviews on the effect of the age at measles vaccination have been published [2-5]. Two reviews by Nic Lochlainn et al focus at children who receive the first dose of measles containing vaccine (MCV1) below 9 months of age. They report that seroconversion after MCV1 increases with age, and that seropositivity after a second dose is high and did not depend on age of MCV1. However, some evidence suggested that MCV1 below 9 months of age resulted in lower antibody titres and a faster decline after one or two subsequent doses of MCV than when measles vaccination is started at age 9 months or older.[6] Epidemiological data reviewed by Carazo et al comparing one-dose vaccine effectiveness for children vaccinated from 6 to ≥15 months indicated older age improved measles seropositivity. This meta-analysis of studies in children of vaccinated mothers showed 96.8% seropositivity after vaccination at 12 months of age, versus 97.6% after vaccination at 13-14 months.[2] The review by Hughes et al looked at whether measles vaccine effectiveness (VE) waned over time, and if so, whether this differed between measles-eliminated and measles-endemic settings. In measles-endemic settings, one-dose VE increased by 1.5% for every month increase in age at MCV1, and no evidence of waning VE was found. Only three papers from elimination settings were included. These studies indicated two-dose VE estimates increased with increasing age at MCV1 and decreased as time since MCV increased.

In The Netherlands, early extra MMR vaccination as a novel control measure was conducted during the outbreak of 2013-2014. All infants between 6 and 12 months of age living in municipalities with vaccination coverage below 90% were invited for an early extra MMR vaccination. Those who were vaccinated before the age of 14 months had a lower measles infection risk than unvaccinated infants. The vaccine effectiveness was 94% (95%CI 79-98%). Part of the effect was, however, caused by herd immunity. Vaccinated infants were more likely to be surrounded by vaccinated individuals. The vaccine effectiveness decreased to 71% (95%CI -72-95%) when adjusted for religion and sibling's vaccination status [7]. Almost 80 children who received an early extra measles vaccination between 6 and 12 months of age during the latest measles epidemic have been studied up to 4 years of age to measure the effect on antibody responses and immune protection. These children showed a slightly stronger waning of measles specific antibody concentrations over time (between 2 and 4 years of age) than children with a first MMR dose at age 14 months. Especially children vaccinated below 9 month of age had lower neutralizing antibody concentrations at four years of age compared with infants vaccinated at a later age, despite an additional vaccination at 14 months of age. For 11.1% of these children, antibody levels at 4 years of age had dropped below the cut off for clinical protection. [6].

In conclusion, early MMR vaccination (<12 months of age) provides immediate protection in the majority of infants but the susceptibility to measles virus infection among early vaccinated individuals may increase with age, consequently herd immunity in the population might be adversely impacted in the long term. Therefore early MMR vaccination should only be applied in an outbreak situation, when the risk of measles for unvaccinated children is high.

Clustering of unvaccinated individuals leads to increased risk of measles outbreaks with introduction of measles virus
The high infectiousness of measles results in a high level of herd immunity of 95% needed to achieve elimination. However, although the overall level of immunity in the population as a whole may be above the herd immunity threshold, outbreaks can still occur in clusters of unvaccinated people.

In 2016/17, the third Pienter-study was conducted primarily aimed to assess the population immunity against (candidate) vaccine-preventable and/or emerging diseases in The Netherlands.[8] In the national cohort, overall measles weighted seroprevalence was 97.0% (95% CI 96.4-97.5), and estimates did not differ significantly between sexes (men: 96.9% and women: 97.1%). Seroprevalence was estimated to be approximately 90% in infants shortly after birth, but declined to 10% from four months of age and was near zero up until the eligible age of the first dose of MMR at 14 months (figures). From there, geometric mean concentration (GMC) increased rapidly from below 0.12 international units (IU)/mL - which is considered the level for protection, depicted by the dashed line in the figure - to 2.0 IU/mL (for comparison, that is half of the concentration after natural infection, see for instance GMCs in persons 50 years and older) and waned to 1.0 IU/mL at 9 year of age, the current eligible age for the second MMR

shot. Likewise, seroprevalence increased steeply after 14 months of age and ranged between 92-99% until age 9 years. Due to administration of the second MMR shot, GMC slightly increased at 9 years of age and the downward slope thereafter was less steep, i.e., indicating a slower rate of waning after the second shot. Seroprevalence remained above 95% until 40 years of age, and reached 100% in pre-vaccine age cohorts, accompanied by a sharp rise in GMC in these groups.

In the low vaccination coverage (LVC) cohort - consisting of individuals from randomly selected municipalities situated in the Bible belt - overall seroprevalence was similar to the national cohort (96.8% [95% CI 95.2-97.9]), as well as to that in sexes (men: 96.5% and women: 97.0%). Despite large similarities with regards to most age groups in the national cohort, seroprevalence and GMC was higher in infants within their first half year after birth, reflecting the higher concentration of maternal antibodies from infants of mothers naturally exposed to measles. Also, both seroprevalence and GMCs were substantially lower in the age groups after the MMR-1 eligible age of 14 months until 4 years in the LVC cohort, but reach nearly 100% in the age groups thereafter. Hence, high levels of immunity in those from 4 years and older in 2016/17 (when the Pienter 3 study was conducted), coincides with exposure to the pathogen during the large outbreak in 2013/14 for most of the individuals in this cohort.

Figure 1 Measles weighed seroprevalence (bars) and geometric mean concentration (GMC) (line), both with 95% confidence intervals/envelop, by age groups (months and years) in the general Dutch population, from the Pienter 3 study (2016/17). The dashed line is considered the level for protection (0.12 IU/mL).
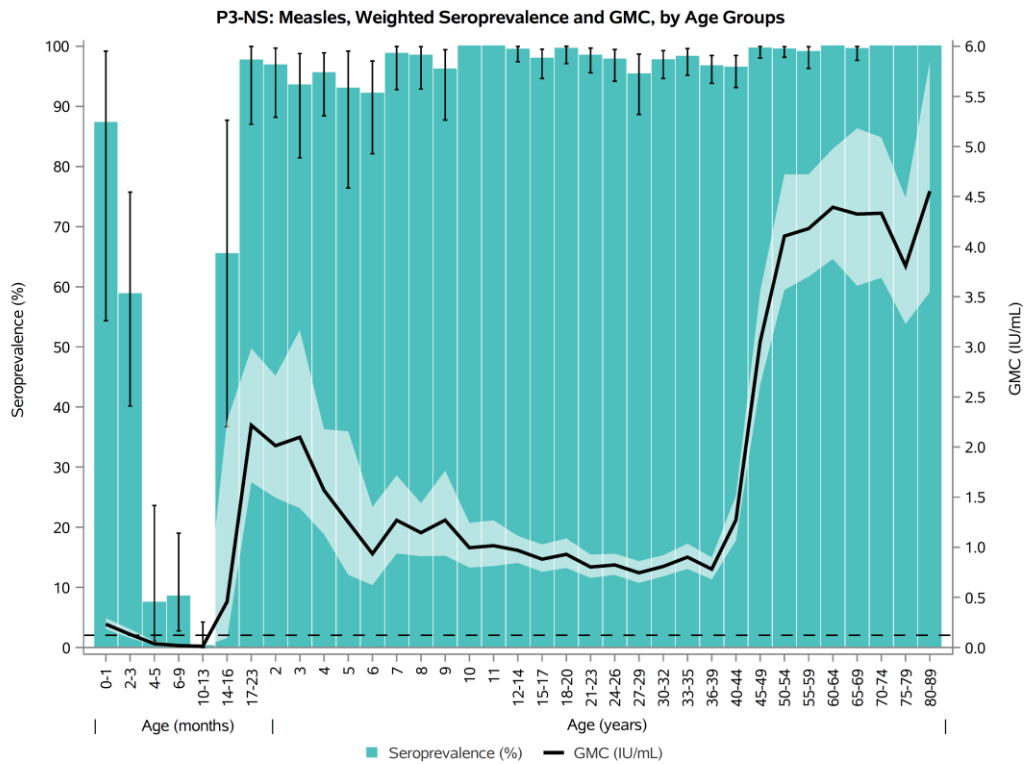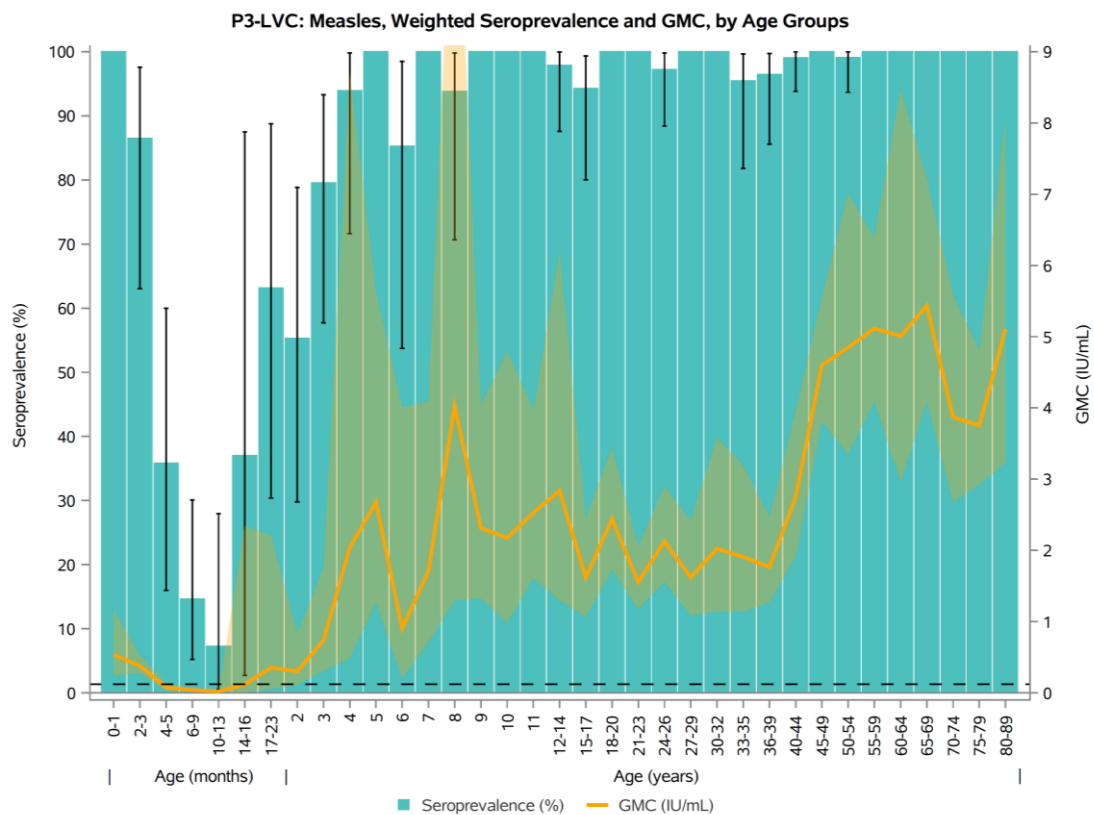
Figure 2 Measles weighed seroprevalence (bars) and geometric mean concentration (GMC) (line), both with 95% confidence intervals/envelop, by age groups (months and years) in the low vaccination coverage municipalities, from the Pienter 3 study (2016/17). The dashed line is considered the level for protection (0.12 IU/mL).

The cohort of susceptible children in the orthodox protestant community will increase with every year without measles outbreaks. The inter-epidemic interval before the 1999-2000 epidemic was ~6 years, and this interval increased to ~14 years before the last epidemic in 2013-2014. This was also reflected in the median age of reported cases which was 10 years in 2013-2014, i.e., four years higher compared with 1999-2000.[9] The higher median age of cases reporting during the 2013-2014 epidemic was also partly caused by the lower incidence of cases below 8 years of age compared with the incidence of cases below 8 from the 1999-2000 outbreak. A plausible explanation could be the improved vaccination coverage among orthodox protestants.[10] An increase in the vaccination coverage among orthodox protestants may lead to longer inter-epidemic periods, resulting in future outbreaks with older age groups affected, which will lead to more complications.

The risk of an outbreak is influenced by the size of the cluster, the number of susceptible individuals, the level of social interaction between unvaccinated individuals and the vaccination rate.[11] Surveillance data indicate that most imported cases of measles cause no or limited onward transmission.[12] However, importation of measles can lead to outbreaks when the number of susceptibles and social interaction between them is high. In The Netherlands this is periodically observed in orthodox protestant communities, and sporadically in other

communities, like the anthroposophical community where an outbreak with 99 reported cases occurred in 2008.[13] Changes in vaccination coverage are monitored as a decrease in coverage in populations that are clustered, and could have implications for future measles outbreaks. Recent research shows that in the G4-cities (Amsterdam, Rotterdam, The Hague and Utrecht) MMR coverage is lower for children from families with a migration background. The largest difference was observed for the combined group of children with a Moroccan or Turkish background, where MMR coverage at age 2 years was 5% lower compared to children from families without migration background.[12] Clustering of unvaccinated children with a migrant background in combination with a potentially higher risk of introduction of measles e.g. after visit to countries where measles is still endemic could increase the risk of outbreaks. However, up to now surveillance data do not indicate outbreaks of measles in communities with a migrant background.

Children with primary vaccine failure after the first dose of MMR are susceptible for a relative long period as the interval between the first and second MMR dose is almost 8 years
The percentage of children with primary vaccine failure after MMR vaccination is approximately 3% (range 2-12%) if immunized at/around 1 year of age.[1, 14] This percentage is lower if children are vaccinated at an older age and if children are vaccinated twice.[1] Studies indicate the age of the second dose does not affect waning of antibody levels over time. Following MMR2, anti-measles IgG antibodies concentrations decreased with time since last vaccination and this was not influenced by age (6 or 11 years) of MMR2 in a Portuguese study with samples collected using a convenience strategy.[15] Also in a large study performed in the US, two schedules for MMR2 were compared (4-6 years and 10-12 years). In both groups titers decreases significantly over time, but when children were 15 years of age, no significant differences were present between GMTs of both groups.[16]
The interval between the first and second dose of MMR determines the number of susceptible children with primary vaccine failure after the first dose.

In the 2013/2014 outbreak 6% of the 2700 reported cases was vaccinated. Of the 141 vaccinated cases, 89% (n=125) had been vaccinated once. Around two-third of these (68%; n=85) were between 14 months and 8 years of age, and half of them (n=61) was between 4 and 8 years of age. This shows that reducing the age of the second dose of MMR has the potential to prevent measles cases in children during an outbreak.

Persons opting out of the NIP have a high risk of measles infection in case of an outbreak, and run a higher risk for complications when they get measles at adult age
Measles virus is one of the most contagious pathogens known, and mostly affected school-age children in the pre-vaccination era. The risk of serious complications and death is increased in children younger than 5 years and adults older than 20 years [1]. In the last outbreak in 2013/2014 the overall hospitalization rate was 7%, and was higher in adults (18-40 years 14%, >40 years 25%).[17] Compared to the nationwide outbreaks, in the post outbreak period the median age is

higher and ranged from 17 to 32 years in the different years. As mentioned in the discussion of issue ii, an increase in the vaccination coverage among orthodox protestants may lead to longer inter-epidemic periods, resulting in future outbreaks with older age groups affected, which will lead to more complications.

3.10.6 Conclusions and suggestions for the request for advice from the Health Council

A national elimination strategy is possible and effective for measles. However, given the relative high numbers of vaccination rejection in orthodox protestants who cluster geographically and socially, reintroduction of measles virus resulting in outbreaks in municipalities with a low vaccination coverage remains a possibility and must be taken into account.

In the case of an outbreak, additional measures are needed to protect children too young to be vaccinated. Previously, additional early MMR vaccination of infants between 6 and 12 months of age in areas with a vaccination rate below 90 percent was shown to be successful and could be applied again.

The second dose of measles vaccine, now administered at nine years of age, is primarily given as a second change to induce immunity in children who did not respond to the first dose. Therefore, it could be considered to advance it and thus reduce the number of susceptible children during an outbreak. An overall better protection of toddlers and young children could thereby be achieved.

3.10.7 References

1. Strebel, P.M., et al., *Measles Vaccines*, in *Plotkin's Vaccines*. 2018, Elsevier: Philadelphia, PA. p. 579-618.
2. Carazo, S., et al., *Effect of age at vaccination on the measles vaccine effectiveness and immunogenicity: systematic review and meta-analysis.* BMC Infect Dis, 2020. **20**(1): p. 251.
3. Hughes, S.L., et al., *The effect of time since measles vaccination and age at first dose on measles vaccine effectiveness - A systematic review.* Vaccine, 2020. **38**(3): p. 460-469.
4. Nic Lochlainn, L.M., et al., *Immunogenicity, effectiveness, and safety of measles vaccination in infants younger than 9 months: a systematic review and meta-analysis.* Lancet Infect Dis, 2019.
5. Nic Lochlainn, L.M., et al., *Effect of measles vaccination in infants younger than 9 months on the immune response to subsequent measles vaccine doses: a systematic review and meta-analysis.* Lancet Infect Dis, 2019.
6. Brinkman, I.D., et al., *Early Measles Vaccination During an Outbreak in the Netherlands: Short-Term and Long-Term Decreases in Antibody Responses Among Children Vaccinated Before 12 Months of Age.* J Infect Dis, 2019. **220**(4): p. 594-602.
7. Woudenberg, T., et al., *Effectiveness of Early Measles, Mumps, and Rubella Vaccination Among 6-14-Month-Old Infants During an Epidemic in the Netherlands: An Observational Cohort Study.* J Infect Dis, 2017. **215**(8): p. 1181-1187.

8. Verberk, J.D.M., et al., *Third national biobank for population-based seroprevalence studies in the Netherlands, including the Caribbean Netherlands.* BMC Infect Dis, 2019. **19**(1): p. 470.

9. Woudenberg, T., et al., *Large measles epidemic in the Netherlands, May 2013 to March 2014: changing epidemiology.* Euro Surveill, 2017. **22**(3).

10. Spaan, D.H., et al., *Increase in vaccination coverage between subsequent generations of orthodox Protestants in The Netherlands.* Eur J Public Health, 2017. **27**(3): p. 524-530.

11. Klinkenberg, D., et al., *[No scientific lower threshold for compulsory vaccination].* Ned Tijdschr Geneeskd, 2020. **164**.

12. Schurink-van 't Klooster, T. and H.E. de Melker, *The National Immunisation Programme in the Netherlands. Surveillance and developments in 2019-2020*. 2020, RIVM: Bilthoven.

13. Hahne, S., et al., *Measles outbreak, the Netherlands, 2008.* Emerg Infect Dis, 2010. **16**(3): p. 567-9.

14. Haralambieva, I.H., et al., *Current perspectives in assessing humoral immunity after measles vaccination.* Expert Rev Vaccines, 2019. **18**(1): p. 75-87.

15. Goncalves, G., et al., *Persistence of measles antibodies, following changes in the recommended age for the second dose of MMR-vaccine in Portugal.* Vaccine, 2015. **33**(39): p. 5057-63.

16. LeBaron, C.W., et al., *Persistence of measles antibodies after 2 doses of measles vaccine in a postelimination environment.* Arch Pediatr Adolesc Med, 2007. **161**(3): p. 294-301.

17. Woudenberg, T., et al., *Additional Evidence on Serological Correlates of Protection against Measles: An Observational Cohort Study among Once Vaccinated Children Exposed to Measles.* Vaccines (Basel), 2019. **7**(4).

3.11 Rubella

3.11.1 History of vaccination against rubella

In 1974 a stand-alone single-dose live-attenuated rubella vaccine was introduced in the NIP for girls at 11 years of age. In 1987 the stand alone vaccine was replaced by the MMR (measles-mumps-rubella) combination vaccine, which is since then given to children at the age of 14 months and at 9 years. So, girls from birth cohorts 1963 to 1977 were offered rubella vaccine at the age of 11 years, all children from birth cohort 1978 and beyond were offered MMR vaccine at 9 years, and from cohort 1986 also at 14 months. [1] The MMR vaccine used in The Netherlands includes the RA 27/3 strain.

3.11.2 Goal of vaccination against rubella

The main goal of vaccination against rubella is to prevent infections in unborn children (and therefore pregnant women), as these can lead to death and disabilities in the children. This can be achieved by maintaining herd immunity in The Netherlands in combination with individual protection of future pregnant women through vaccination. Vaccination also contributes to the international goal of eliminating rubella and preventing onward spread from The Netherlands.

3.11.3   *Epidemiology of rubella in The Netherlands*
Before the introduction of rubella vaccination (1974 and 1987) the
annual number of rubella notifications varied between several hundred
to over 5,000 (figure 1). Large outbreaks occurred every 4 to 6 years.
By 1998, the number of notifications had fallen to almost 20. From 1999
to 2003, the number decreased further to 1-12 per year. In 2004-2005
an epidemic of rubella occurred, predominantly in the bible belt. More
than 400 cases of rubella were reported during this period. This
epidemic caused congenital rubella syndrome (CRS) in 11 children. Two
unborn children died from the disease.[2] After the outbreak of 2004-
2005, the number of reports decreased again. In 2013, the number of
notifications was 57, mostly related to a limited outbreak at an orthodox
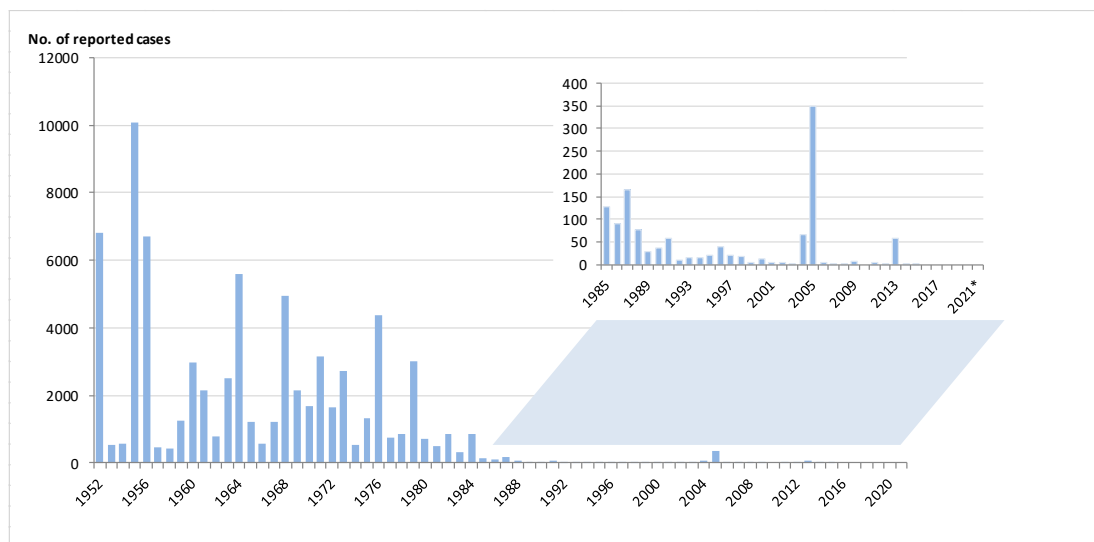protestant primary school.

Figure 1 Annual reported rubella cases since 1952

Until 1997, the number of hospital admissions was around ten per year,
in the period 1999-2017 the number of hospital admissions varied
between zero and three per year. Between the years 1997 and 2019,
there were two reports of death due to rubella, in 2002 and 2005.[3]

3.11.4   *Assessment of the vaccination against the six criteria, issues identified*
Is the protection adequate for all those intended to be protected?
Rubella generally manifests as a mild infection, but when infection
occurs around conception or in early pregnancy, there is high risk of
miscarriage, fetal death or CRS in the newborn. CRS is prevented as
women are offered two doses of MMR vaccine before child bearing age.
However, a low vaccination coverage in the "bible belt" results in regular
outbreaks, even though the basic reproduction number (R0) of 6-7 for
rubella is lower than that of measles.

Issue related to criterion 1
Unborn children of pregnant women without immunity against rubella
and living in areas with low vaccination coverage are at risk of
complications of rubella in case of an outbreak.

1. Is the applied vaccination strategy optimal?
Yes. The rubella vaccine is a highly immunogenic vaccine, and after one dose of MMR vaccine only 1% of the children do not respond to the vaccine (primary vaccine failures). Some of these children do respond to a second MMR dose.

Elimination is feasible and requires a vaccination coverage >84%. The presence of clusters of unvaccinated individuals poses an increased risk for development of an outbreak after introduction of the virus in The Netherlands. There is a trend towards an increased acceptance of vaccination among members of the protestant orthodox reformed community reducing the number of unvaccinated individuals in these clusters.[4]

2. Does the programme include too much?
Maybe. The second dose can result in seroconversion in children with primary vaccine failure after the first MMR dose. But primary vaccine failure is rare as the seroconversion after one dose is 99%. The positive effect of a second dose on waning of antibody concentrations is minor and transient. Given the high seroconversion rate after one dose, which is above the herd immunity threshold, a second dose is not required per se to increase the level of protection in the population.

Issue related to criterion 3
Seroconversion after one dose of rubella vaccine is very high and a second dose is not needed to increase the level of protection.

4. Does the programme include too little?
No. Two vaccine doses is sufficient to protect the general population against rubella and infants against CRS.

5. Is the timing of immunisations using combination vaccines optimal or at least acceptable?
Timing of current immunisation schedule for MMR vaccine (doses at 14 months and 9 years of age) is acceptable for rubella. Immunologically it is important that immunisation is not given too young, i.e., before 12 months, and it should be administered before childbearing age. The current schedule meets those criteria.

6. Are there important drawbacks of the NIP? For the population as a whole? For those who opt out? How are these drawbacks to be weighed against the advantages of the programme and its components?

The current rubella vaccination programme protects the population as a whole including people that opt out for vaccination. In specific regions with a low vaccination coverage such as the Bible belt, however, too many individuals opt out resulting in a vaccination rate that is too low (<84%) to provide herd immunity, increasing the chance of outbreaks. As long as outbreaks do not occur, the number and age of susceptible persons will increase. This group could be at risk of a new outbreak due to imported cases of rubella, as internationally levels of rubella vaccination coverage and incidence vary. This is particularly concerning for women and girls of child bearing age within the orthodox protestant

community due to the risk of CRS. This issue was already identified in relation to criterium 1.

3.11.5   *Exploration of the issues against the available evidence*
Unborn children of pregnant women without immunity against rubella and living in areas with low vaccination coverage are at risk of complications of rubella in case of an outbreak
For the vast majority of the country, an elimination strategy is possible and effective. The general population is well protected against infection with rubella virus, partly through vaccination. However, as geographical and social clustering of orthodox protestants who reject vaccination is present, reintroduction of rubella virus resulting in outbreaks in municipalities with a low vaccination coverage must always be taken into account.

Preliminary analyses of the Pienter 3 study conducted in 2016/17 indicate that the Dutch population is well protected against rubella, with a high overall seroprevalence of protective antibodies of 94.8% (95% CI 94.0-95.5%). Highest susceptibility was seen in children under 14 months of age, prior to the administration of the 1st dose of a rubella containing vaccine (Figure 2A). Analyses indicated that susceptibility was higher among individuals in municipalities with low vaccination coverage than in the general Dutch population, with an overall seroprevalence of rubella protective antibodies of 86.6% (95% CI 80.7-91.2%).The highest susceptibility was seen among children under 12 years of age within these municipalities, born after the last rubella epidemic in 2005 (Figure 2B).

With a low rubella incidence in The Netherlands, a considerable pool of rubella susceptible individuals will accumulate in areas with a low vaccination coverage. This situation requires ongoing sensitive surveillance monitoring, as , a rubella epidemic is to be expected in these areas.[5] The long interval between the rubella outbreaks and hence the potentially higher age at infection creates susceptibility among women of childbearing age. If infections during pregnancy occur, it can lead to miscarriages, stillbirths and CRS cases. The cohort of unvaccinated children who were born just after the last outbreak were 16-17 years of age in 2021.

Following Dutch policy, pregnant women are offered screening for rubella antibodies when they are unvaccinated or when their vaccination status is unknown. Vaccination is offered post-partum to women with no or insufficient antibodies.[6] This policy offers unprotected women, e.g. women born in countries without universal rubella vaccination, or women whose parents refused vaccination for them, the chance of getting vaccinated before a subsequent pregnancy.

After the 2004/2005 outbreak, the feasibility of a rubella screening and vaccination programme for unvaccinated young women was assessed. This programme proved to be an inefficient strategy for rubella protection as uptake and acceptance of vaccination was low and in the end only 0.9% (95% CI 0.1-2.5) of the target population was given protection by the programme. [7]
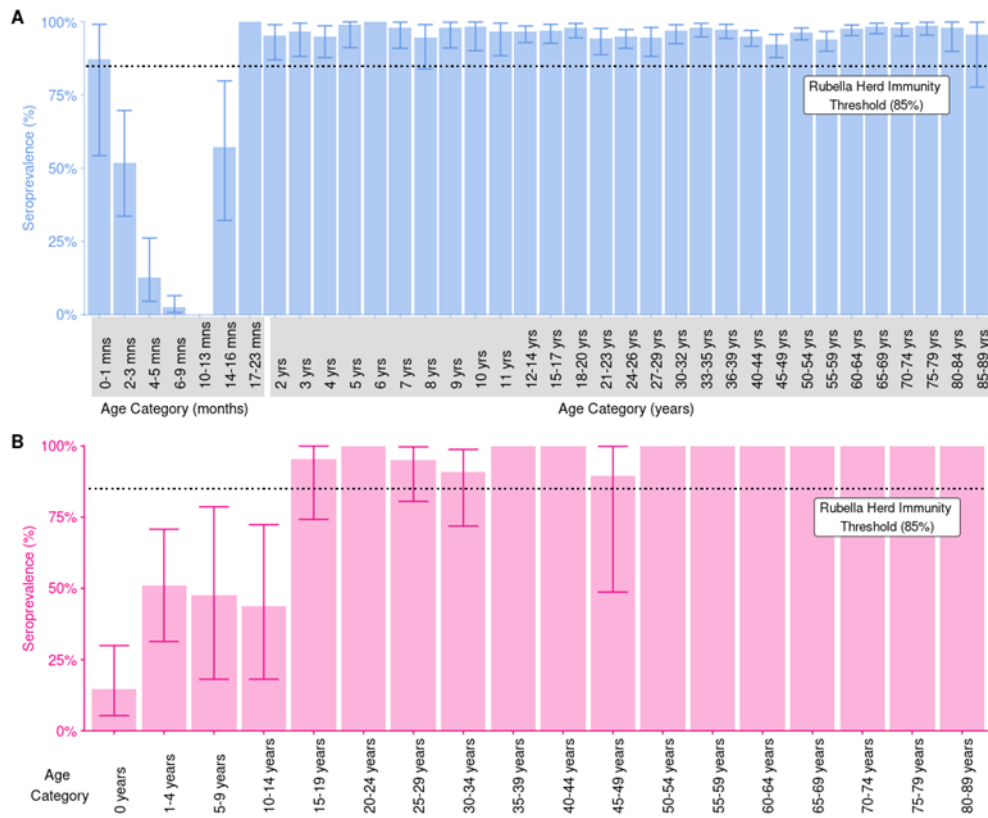
Figure 2 Preliminary analyses of weighted seroprevalence of rubella IgG antibodies (cut-off is ≥10 IU/mL) with 95% confidence intervals, by age category in The Netherlands, from Pienter 3 in 2016/17. Panel A: Results for the general Dutch Population (N=5,146); Panel B: Results for the population in municipalities with low vaccination coverage (N=1,355).

Seroconversion after one dose of rubella vaccine is very high and a second dose is not needed to increase the level of protection
A recent meta-analysis of immunogenicity data of rubella containing vaccines showed 99% seroconversion (95% CI: 98-99%) after a single dose in children, independent of co-administration with other vaccines. Seropositivity after two doses was 100% (95% CI: 99-100%). In this review the pooled vaccine effectiveness estimate for RA 27/3 strain (one or two doses) against rubella was 97% (95% CI: 92–99%) based on four studies.[8] The Pienter 2-study showed that the second rubella vaccination induced only a small increase in antibody concentration, but resulted in a slower decline compared with the first vaccination.[5] This was also observed in the Pienter study in Caribbean Netherlands.[9] However, a longitudinal study from Belgium showed that a second dose at age 4-10 years had only a minor and transient effect on anti-rubella waning titers.[10]

A second dose of rubella vaccine is most likely not needed to achieve herd immunity in the general population.

Discussion and potential resolution of the issues
The main issue is the susceptibility among women of childbearing age in geographically and socially clustered communities who reject vaccination

which poses a risk when rubella virus is introduced. This issue could potentially be resolved by increasing vaccine uptake in these populations. There is however no clear solution on ways to achieve this.

3.11.6   *Conclusions and suggestions for the request for advice from the Health Council*
Already after one dose rubella vaccine is highly effective in preventing rubella infection and congenital rubella syndrome. To mitigate the risk of future outbreaks in clustered populations with low vaccination acceptancy, the uptake among women in such populations should be improved.

3.11.7   *References*
1.   Reef, S.E. and S.A. Plotkin, *Rubella Vaccines*, in *Plotkin's Vaccines*. 2018, Elsevier: Philadelphia, PA. p. 970-1000.
2.   Hahne, S., et al., *Rubella outbreak in the Netherlands, 2004-2005: high burden of congenital infection and spread to Canada.* Pediatr Infect Dis J, 2009. **28**(9): p. 795-800.
3.   Schurink-van 't Klooster, T. and H.E. de Melker, *The National Immunisation Programme in the Netherlands. Surveillance and developments in 2019-2020*. 2020, RIVM: Bilthoven.
4.   Spaan, D.H., et al., *Increase in vaccination coverage between subsequent generations of orthodox Protestants in The Netherlands.* Eur J Public Health, 2017. **27**(3): p. 524-530.
5.   Smits, G., et al., *Seroprevalence of rubella antibodies in The Netherlands after 32 years of high vaccination coverage.* Vaccine, 2014. **32**(16): p. 1890-5.
6.   *LCI Richtlijn Rodehond, bijlage Rubellascreeningsbeleid bij zwangere vrouwen*. 2017; Available from: https://lci.rivm.nl/richtlijnen/rodehond.
7.   Ruijs, W.L., et al., *Feasibility of a rubella screening and vaccination programme for unvaccinated young women.* Epidemiol Infect, 2009. **137**(9): p. 1319-22.
8.   van den Boogaard, J., et al., *Immunogenicity, duration of protection, effectiveness and safety of rubella containing vaccines: A systematic literature review and meta-analysis.* Vaccine, 2021. **39**(6): p. 889-900.
9.   Vos, R.A., et al., *Seroepidemiology of Measles, Mumps and Rubella on Bonaire, St. Eustatius and Saba: The First Population-Based Serosurveillance Study in Caribbean Netherlands.* Vaccines (Basel), 2019. **7**(4).
10. Carryn, S., et al., *Long-term immunogenicity of measles, mumps and rubella-containing vaccines in healthy young children: A 10-year follow-up.* Vaccine, 2019. **37**(36): p. 5323-5331.

3.12 Cancers caused by HPV infection

3.12.1 History of vaccination against HPV-related cancers

A vaccine against cervical cancer caused by human papilloma virus (HPV) infection was introduced into the NIP in 2010 for girls. Girls were invited for vaccination with three doses (at 0, 1 and 6 months) at the age of 12-13 years. Additionally, a catch-up campaign was launched in which girls up to and including birth cohort 1993 were invited for vaccination with three doses. Since 2014, i.e. for girls born from 2001 onwards, a switch to a two-dose regimen (at 0 and 6 months) was made for girls up to the age of 15 years. Older girls are still advised to receive three doses. From 2022 onwards, following the advice of the Health Council, the scope of HPV vaccination was broadened to include cancers caused by HPV infection in general. Consequently, HPV vaccination will be offered as gender-neutral. Boys and girls will be invited for HPV vaccination at the age of 9-10 years. Moreover, a catch-up campaign will start in which all boys, and girls who have not or have been incompletely vaccinated will be invited for HPV vaccination until the age of 18 years.

The vaccine Cervarix® has been used since NIP introduction of the vaccine. This vaccine is a bivalent vaccine against oncogenic HPV types 16 and 18, which are the most common HPV-types to cause HPV-related cancer.

3.12.2 Goal of vaccination against HPV-related cancers

To prevent HPV-related cancer, i.e. cancer of the cervix, vulva, vagina, anus, penis and oropharynx.

3.12.3 Epidemiology of HPV-related cancers in The Netherlands

Infection with human papilloma virus

HPV is a highly contagious virus that can be transmitted via sexual contact but also via skin to skin contact [1]. Per-partner HPV transmissibility is estimated at 60% [1]. The average lifetime probability of acquiring HPV among those with at least one opposite sex partner is estimated to be 85% for women and 91% for men [2]. More than 80% of the men and women acquire HPV by the age of 45 years [2].

Based on the evidence for oncogenic properties, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 are considered high risk HPV (hrHPV) types [3]. Some low risk HPV (lrHPV) types, such as HPV types 6 and 11, can cause benign anogenital warts. The majority of cervical HPV infections are cleared or suppressed within 1 to 2 years of exposure [4]. Persisting hrHPV infection can cause several types of cancer after many years.

HPV-related cancers and other diseases

A (persistent) HPV infection is a necessary factor in the development of cervical intraepithelial neoplasia (CIN) and cervical cancer and partly attributes to cancers of the vagina, vulva, anus, penis and oropharynx [5-12]. In the Netherlands, the incidence of HPV-related cancers ranged between 0.54 per 100,000 for vulva cancer and 8.58 per 100,000 for cervical cancer in 2020 (Figure 1). An increase in incidence since 2000 was observed for cervical, vulvar, penile and anal cancer, while the

incidence of oropharyngeal, mouth and vagina cancer was relatively stable (Figure 1). Moreover, a significant increase in HPV-positive oropharyngeal cancers was observed in the period 2000-2015 [10]. Yearly, around 1600 HPV-related cancers are diagnosed among women and around 800 among men with corresponding estimated number of deaths of around 450 for women and 200 for men [13, 14].

Infection with non-oncogenic HPV types 6 and 11 can cause genital warts (condylomata acuminata) and laryngeal papillomatosis [15]. Genital warts are harmless and common, but can be painful, itchy and uncomfortable. Laryngeal papillomatosis is a rare but severe condition which mainly causes respiratory complaints. Treatment strategies depend on complaint severity [15].
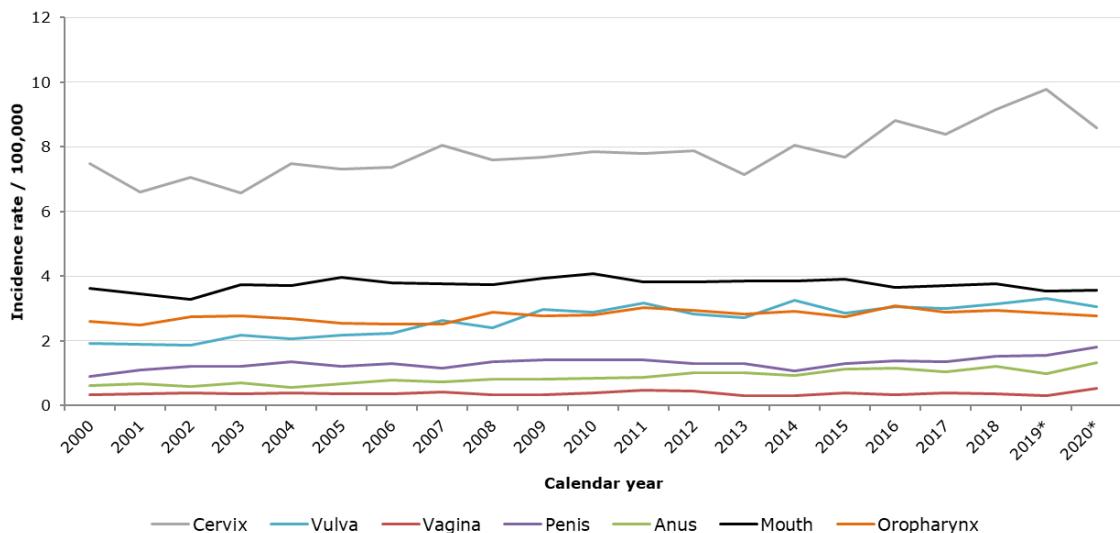

*Figure 1 Incidence rates^a (per 100,000, standardized by European standardized rates) of cervical-, vulvar- and vaginal cancer for women, penile cancer for men, and anal-, mouth/oral- and oropharyngeal cancer for men and women in The Netherlands, 2000-2020. *Preliminary incidence rates. ^{a}Incidence rates were obtained from The Netherlands Cancer Registry, IKNL (iknl.nl/nkr-cijfers, accessed Apr 20, 2021).*

3.12.4   *Assessment of the vaccination against the six criteria, issues identified*
1. Is the protection adequate for all those intended to be protected?
Over 200 HPV-types are known of which thirteen types are considered hrHPV types based on their oncogenic properties [3]. Three HPV-vaccines are licensed in Europe: a bivalent vaccine (Cervarix®) against hrHPV types 16 and 18, a quadrivalent vaccine (Gardasil®) against hrHPV types 16 and 18 and against the lrHPV types 6 and 11, and a nonavalent vaccine (Gardasil9®) against seven hrHPV types (HPV types 16, 18, 31, 33, 45, 52 and 58) and two lrHPV types (HPV types 6 and 11). These vaccines are all licensed for prevention of cervical cancer and anal cancer, and premalignant lesions of the cervix, anus, vulva and vagina. The nonavalent vaccine is also licensed to prevent vaginal and vulvar cancer. Additionally, the quadrivalent and nonavalent vaccine are licensed to prevent genital warts. None of the vaccines are licensed for prevention of penile cancer or its pre-malignant lesions, or of

oropharyngeal cancer [16-18]. The effectiveness of the vaccines is higher if administered at a lower age, i.e. if administered before sexual debut [19]. In 2019, the Health Council of The Netherlands concluded that the evidence was insufficient for a preference of either vaccine [15]. The bivalent vaccine is currently used in The Netherlands after a European tendering procedure.

Issues related to this criterion
None of the vaccines induce a response to all oncogenic HPV-types. Will the effectiveness against only vaccine targeted HPV types be sufficient to prevent HPV-related cancer? Cross-protection against non-vaccine hrHPV types for the bivalent and quadrivalent vaccine is reported. Is the cross-protective effect against non-vaccine hrHPV types considered sufficient to prevent HPV-related cancer related to non-vaccine hrHPV types? Or should we aim at using a vaccine that targets most or all hrHPV types?

2. Is the applied vaccination strategy optimal?
To prevent HPV-related cancers, boys and girls should be vaccinated with HPV vaccines. Only girls are vaccinated up to 2022. In 2019, the Health Council of The Netherlands advised to incorporate gender neutral HPV-vaccination in the NIP and to lower the age at which HPV vaccination is offered from 12-13 years to 9-10 years [15]. This will be implemented from 2022 on. At the same time, a catch-up campaign will start in which all boys and girls who have not been vaccinated or are incompletely vaccinated aged up to 18 years are invited for HPV vaccination. The aim is to extend the catch-up campaign up to the age of 26 years by the end of 2022.

For girls, the HPV vaccination coverage has been low in comparison with other target diseases covered by the NIP. The coverage varied between 45.5% and 63.1% [20]. The lowest vaccination coverage of 45.5% was observed for girls born in 2003 and 2004 [21]. An increase is observed for girls born in 2005 and 2006 with an HPV vaccine coverage of 53.0% and 63.1% respectively [21]. The potential increasing trend is promising and the preliminary vaccine coverage data for girls born in 2007 and 2008 seems to support the positive trend (unpublished data) even though the COVID-19 pandemic challenged (HPV) vaccine provision. The global target for HPV vaccine coverage to eliminate cervical cancer as a public health problem is 90% for girls by the age of 15 years by 2030 [22].

Issues related to this criterion
Low vaccination coverage in girls.

3. Does the programme include too much?
No, not yet. Since 2014, the number of doses for girls aged <15 years has been reduced to two (at 0 and 6 months) instead of three (at 0, 1 and 6 months). For older girls, the third dose is still administered to elicit an optimal immune response.
HPV vaccination in a one-dose regimen has not been registered by the European Medicine Agency (EMA). Nevertheless, several studies suggested that a single dose of an HPV vaccine may be efficacious [23]. Within a Dutch cross-sectional study it was observed that a one dose

schedule of the bivalent vaccine is immunogenic, but the antibody responses were lower compared with a >1 dose schedule [24]. In the Costa Rica HPV Vaccine Trial (CVT) it was observed that 100% of the women who received the bivalent vaccine at the age of 18 to 25 years remained seropositive at years 9 and 11 after vaccination, regardless of the number of doses received (i.e. one, two or three doses) [25].

Sankaranarayanan *et al.* showed that girls vaccinated at the age of 10 to 18 years with a single dose of the quadrivalent vaccine had lower antibody concentrations compared with girls that received two- or three doses. These antibody levels remained stable up to 36 months after vaccination [26]. Toh *et al.* showed lower neutralizing antibody titers against HPV types 16, 18, 6 and 11 after six year in girls who received a single dose of the quadrivalent vaccine compared with girls who received two or three doses [27]. In a study conducted in India, at 10 years after vaccination, a vaccine efficacy of 63.5% (95% CI 51.2, 73.1) was observed against incident infections and of 95.4% (95% CI 85.0, 99.9) against persistent infections with HPV types 16 and 18 in women who received a single dose of the quadrivalent vaccine at the age of 10-18 years [28]. Corresponding vaccine efficacies in two- and three-dose recipients were 67.7% (95% CI 55.2, 77.2) and 93.1% (95% CI 77.3, 99.8), and 66.4% (95% CI 53.6, 76.3) and 93.3% (95% CI 77.5, 99.7), respectively. Also no evidence for a better or worse vaccine effectiveness against CIN2+ or CIN3+ cervical lesions was observed for women after receiving two or three doses of the quadrivalent vaccine compared with one dose in a Danish nationwide study [29]. Six years after vaccination, a single dose of the quadrivalent vaccine was associated with reduced genital prevalence of HPV types 16 and 18, but not other hrHPV types among women aged 16 to 26 years [30]. Vaccine-specific HPV seropositivity was 90% for HPV type 16 and 58% for HPV type 18. A comparison with two- or three dose recipients was not included in the study.

Within a systematic review and meta-analysis by Secor *et al.*, the antibody response against HPV types 16 and 18 at 36 and/or 72 months after vaccination were not non-inferior after a one dose regimen compared with a standard regimen for both the bivalent and quadrivalent vaccine [31]. No single dose data was available for the nonavalent vaccine. It should be noted that for all studies, data from single dose receivers were collected from participants who were supposed to receive two or three doses. The results may therefore not be generalizable to larger populations. Several randomized controlled trials designed to compare a single dose with multiple doses are underway [23]. Recently, on 11 February 2022, the UK Joint Committee on Vaccination and Immunisation (JCVI) published an interim advise in which was agreed that there is now enough evidence to advise a change in the HPV vaccination schedule from a two-dose to a one-dose regimen for children aged up to and including 14 years, and, outside the scope of the UK routine adolescent vaccination programme, to move from a three-dose to a two-dose regimen in those aged 15 years and over [32]. The advice to switch from a two- to one-dose regimen has been based on published and unpublished data on immunogenicity, efficacy (up to at least 10 years) and duration of antibody responses for the bivalent and quadrivalent vaccine [33], and on results presented to the JCVI

regarding immunogenicity and short-to-medium term protection for the nonavalent vaccine [32]. The latter presented results included preliminary results from the DoRIS study [34], the KEN SHE trial [35, 36], and the DEBS [37], and an internal update of a previously published systematic review [38].

Issues related to this criterion
No new issue at present. However, the new developments in the UK where the JCVI recently advised a reduced dose regimen might lead to future consideration of the health council regarding a reduced schedule.

4. Does the programme include too little?
Currently, Cervarix® is used as HPV-vaccine in The Netherlands. This vaccine protects against two (HPV types 16 and 18) of the thirteen hrHPV types. A vaccine against a wider range of hrHPV may be preferred. This issue will be discussed in relation to criterion 1.

Issues related to this criterion
No new issues identified.

5. Is the timing of immunisations using combination vaccines optimal or at least acceptable?
The HPV vaccine is not co-administered with another vaccine. This criterion is therefore not applicable at the moment. However, from 2022 onwards, the age of invitation for the first HPV vaccination will decrease to 9-10 years. Currently, eight-to-nine year-olds are invited for measles, mumps, and rubella (MMR) and diphtheria, tetanus, pertussis (DTP) vaccination. All three HPV vaccines can be administered concomitantly with a booster DTP vaccine without any clinically relevant interference with antibody responses [16-18]. Co-administration of HPV vaccination with MMR vaccination is not contra-indicated but little is known about the vaccine-induced immune response when the HPV and MMR vaccines are given concomitantly. For boys and girls aged 9-10 years, one Municipal Health Service in The Netherlands will apply the first HPV vaccination concomitantly with MMR vaccination and the second HPV vaccination concomitantly with DTP vaccination.

Issues related to this criterion
No new issues identified.

6. Are there important drawbacks of the NIP? For the population as awhole? For those who opt out? How are these drawbacks to be weighed against the advantages of the programme and its components?

HPV type replacement
Since the vaccines are not designed to induce a response to all (oncogenic) HPV types, a theoretical niche may arise for replacement with HPV types that are not included in the vaccine. All vaccines induce an immune response against HPV types 16 and 18 which are involved in the majority of HPV-related cancers. Any type replacement would therefore result in replacements with either oncogenic types that are less often involved in HPV-related cancers or with non-oncogenic HPV

types. A review concluded that so far, studies can neither confirm nor eliminate the possibility for type replacement after HPV vaccination [39].

6.2 Vaccination vs. population cervical cancer screening
From 2023 on, the first girls who were vaccinated with an HPV vaccine will be invited for cervical cancer screening. Since HPV vaccination will reduce the incidence of cervical cancers, the effectiveness and cost-effectiveness of cervical cancer screening may change. The Centre for Population Screening of the National Institute for Public Health and the Environment currently investigates whether the cervical cancer screening programme should be adapted for all women or for vaccinated women only in order to maintain optimal (cost-)effectiveness.

Issues related to this criterion
No new issues identified.

3.12.5   *Exploration of the issues against the available evidence*
The spectrum of HPV vaccines
As mentioned previously, a bivalent vaccine targeted at HPV types 16 and 18 is used as HPV vaccine in The Netherlands. The majority of the HPV-related cancers are attributed to HPV types 16 and 18 (Table 1) [5, 6, 8, 9]. A quadrivalent vaccine that includes hrHPV types 16 and 18 and lrHPV types 6 and 11, and a nonavalent vaccine that includes hrHPV types 16, 18, 31, 33, 45, 52, 58 and lrHPV types 6 and 11 are also licensed by the European Medicine Agency. In 2019, the Health Council of The Netherlands concluded that HPV vaccination protects against HPV infections in both girls and boys and against precursor lesions of cervical cancer in women, and that HPV vaccination is expected to protect against (pre)cancerous lesions of HPV-related cancers in men [15]. The Health Council considered the evidence insufficient for a preference for any of the vaccines [15]. Several new studies regarding vaccine effectiveness against HPV-related cancer and high grade cervical lesions, and regarding HPV immunogenicity and cross-protective effects were published after 2019. These are mentioned below.

Table 1 Estimates of HPV-attribution and HPV type 16/18 attribution of HPV-related cancers. HPV, human papilloma virus

Location of HPV-related cancer	**HPV-attribution (%)**	**HPV type 16/18 attribution (%)**
Cervix	99.7 [40]	70.8 [5]
Vagina	71 [8]	71.2 [8]
Vulva	15.0 [9]	77.1 [9]
Penis	32.2 [6]	72.5 [6]
Anus	88.0 [5]	87.0 [5]
Oropharynx	48.1 [41]	84.9 [5]

Vaccine effectiveness against severe HPV-related disease
Within a large UK register-based observational study, a relative reduction in cervical cancer rates of 87% (95% confidence interval [CI] 72, 94) was observed for a cohort of women invited for vaccination at the age of 12-13 years with the bivalent vaccine according to a three-dose regimen compared with women from unvaccinated cohorts. Risk reductions were lower in cohorts of women invited for HPV vaccination

at the age of 14-16 years (62%, 95% CI 52, 71) and 16-18 years (34%, 95% CI 25, 41) [42]. For CIN3 cervical lesions, the relative risk reduction was 97% (95% CI 96, 98) for vaccinated girls with age of vaccine offer at 12-13 years, 39% (95% CI 36, 41) for those offered vaccination at 16-18 years and 75% (95% CI 72, 77) for those offered vaccination at age 14-16 years [42]. In Finland, a passive long-term follow-up study was performed in women who received either the bivalent or quadrivalent HPV vaccine within a clinical trial setting [43]. Over a 7-year time-period, no cases of HPV-related cancer were observed in 9,529 vaccinated women while 10 cases were observed in 17,838 unvaccinated women with a corresponding vaccine effectiveness of 100% (95% CI 16, 100) against HPV-related cancers [43]. Within a Danish nationwide cohort of all women between 17 and 25 of age, CIN3+ lesions were less common in quadrivalent vaccinated versus unvaccinated women with incidence rate ratios (IRR) of 0.37 (95% CI 0.30, 0.45), 0.38 (95% CI 0.22, 0.66) and 0.38 (95% CI 0.14, 0.98) for women who received three, two and one dose respectively [29]. For CIN2+ lesions, corresponding IRRs were 0.43 (95% CI 0.36, 0.51), 0.49 (95% CI 0.32, 0.76) and 0.34 (95% CI 0.13, 0.87). Up to four years after receival of the third dose of the nonavalent vaccine, vaccine effectiveness against CIN2+ or worse related to HPV types 16, 18, 31, 33, 45, 52, and 58 was 100% (95% CI 79.4, 100) [44]. In the same study, no vulvar or vaginal cancer was observed related to the vaccine-specific HPV types. Approximately eight years after vaccination with the nonavalent vaccine, no cases of cervical high-grade intraepithelial neoplasia were observed in girls vaccinated with a three-dose regimen [45]. Additionally, no penile intraepithelial neoplasia was observed in three-dose vaccinated boys. No unvaccinated group was included for comparison [45]. A reduction of 98.2% (95% CI 93.6, 99.7) for high grade cervical diseases related to HPV 6, 11, 16, 18, 31, 33, 45, 52 or 58 was observed in nonavalent vaccinated girls who were vaccinated three times and were negative for 14 HPV types at baseline [46]. Vaccine efficacy against high grade vulvar and vaginal disease related to the vaccine-specific HPV types was 100% (95% CI 85.7, 100).

Immunogenicity
Schwarz *et al.* showed that the bivalent vaccine is immunogenic up to ten years after a three-dose schedule in girls aged 10-14 years [47]. Models indicated that these levels will persist for at least 20 years [47]. In the Costa Rica HPV Vaccine Trial they observed that 100% of the HPV vaccinated women at the age of 18-26 years remained seropositive for HPV type 16 and 18 at year 9 and 11 after vaccination with the bivalent vaccine, regardless of the number of doses received [25]. Within a Dutch cross-sectional study it was observed that a one-dose schedule of the bivalent vaccine in girls is immunogenic, although both antibody and cellular responses were lower compared with those after a two-dose schedule, which may influence long-term immunity [24]. Long term follow-up data of a clinical trial showed that seropositivity remained up to ten years in boys and girls 9-15 years of age who had received the quadrivalent vaccine [48]. Within a long term follow-up extension study of an immunogenicity and safety study, the nonavalent vaccine elicited a similar antibody response as the quadrivalent vaccine among boys and girls aged 9-15 years, up to at least 7.5 years after vaccination [45].

Additionally, all participants seroconverted for HPV types 31, 33, 45, 52 and 58.

Cross-protective effect
Cross-protection may also prevent lesions caused by hrHPV types which are not included in the vaccine. Cross-protection is mainly investigated for the bivalent and quadrivalent vaccine since the nonavalent vaccine includes the most important hrHPV types, i.e. hrHPV types 16, 18, 31, 33, 45, 52 and 58.

Cross-protective vaccine effect
A recent systematic literature review of randomized controlled trials and observational studies published between 2008 and 2019 shows a consistent statistically significant cross-protective efficacy of the bivalent vaccine against persistent genital 6-month and 12-month infections and CIN2+ lesions related to HPV types 31 and 45 [49]. The strongest effect was observed for 6-month persistent HPV type 31 infections (range 64.6% to 79.1%; maximum follow-up of 4.7 years). No cross-protection was shown in extended follow-up. The quadrivalent vaccine efficacy reached statistical significance for HPV type 31 only (46.2%, 95% CI 15.3, 66.4; follow-up of 3.6 years). Similarly, observational studies found significant effectiveness only against outcomes related to HPV types 31 and 45 for both vaccines. A recent publication of Basu *et al.*, which was not included in the systematic literature review, investigated the vaccine efficacy against incident infections related to HPV types 31, 33 and 45 at 10 years after vaccination with the quadrivalent vaccine. They found vaccine efficacies of 43.5% (95% CI 25.4, 56.5) for single-dose recipients, 54.0% (95% CI 38.5, 66.5) for two-dose recipients and 54.6% (95% CI 38.3, 66.6) for three-dose recipients [28]. Vaccine efficacies against persistent HPV type 31/33/45 infections were 8.8% (95% CI -230.8, 65.7), 8.4% (95% CI -293.3, 65.7) and 38.8% (95% CI -124.4, 80.2) for single-dose, two-dose and three-dose recipients respectively. Beyer *et al.* concluded that, based on CIN3+ outcomes for cervical cancer (irrespective of HPV type) in randomized controlled trials and population-based cohort studies, the bivalent vaccine would be preferred over the quadrivalent vaccine since it has a higher efficacy and effectiveness against such lesions [50].

The cross-protective effect for men was investigated in one randomized controlled trial of the quadrivalent vaccine [49]. No statistically significant cross-protective effect was observed against external genital lesions, anal intraepithelial neoplasia and anal cancer among men who were negative for 14 HPV types (HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) before vaccination.

Cross-protective immunogenicity
A recent systematic literature review assessed the consistency and durability of the cross-protective neutralizing antibody immune responses of the bivalent and quadrivalent vaccines to the non-vaccine HPV types targeted by the nonavalent vaccine, i.e. HPV types 6, 11, 31, 33, 45, 52 and 58 [51]. Fourteen interventional and five observational studies published between 2008 and 2019 were included. It was concluded that the cross-protection antibody/immune response after receival of the bivalent or quadrivalent vaccine is partial as well as lower

than those elicited by the vaccine-specific HPV types. Moreover, long-term data on persistence of the cross-protective neutralizing antibody immune responses are limited and therefore its effect remains yet to be demonstrated.

Vaccine (cross-protective) effects in monitoring data of The Netherlands
In The Netherlands, women are invited for cervical cancer screening at the age of 30 years. The first Dutch women that were vaccinated within the NIP will therefore be invited for screening in 2023. Monitoring the effects of HPV vaccination in The Netherlands is therefore focused on its effects against infection and at its effects on the immune response. Additionally, the early effects of HPV vaccination on outcomes of cervical smears obtained before entry into the cervical cancer screening programme has been investigated.

HPV vaccine effectiveness against infections is monitored within two prospective cohort studies (HAVANA and HAVANA2) [52, 53]. The HAVANA study included women who were either unvaccinated or vaccinated with the bivalent vaccine according to a three-dose regimen at the age of 14 to 16 years. HAVANA2 included girls who were either unvaccinated or vaccinated with the bivalent vaccine according to a two-dose regimen at the age of 12-13 years. Preliminary vaccine effectiveness has been estimated for up to ten years after vaccination within the HAVANA study [20]. Vaccine effectiveness estimates against genital incident and persistent vaccine-type infections were 78.8% (95% CI 69.1, 85.5) and 95.8% (95% CI 86.6, 98.7) respectively. Vaccine effectiveness estimates against genital incident and persistent cross-protective infection related to HPV types 31/33/45 were 49.6% (95% CI 31.6, 62.8) and 64.7% (95% CI 37.8, 79.9) respectively. Cross-protective type-specific vaccine effectiveness up to ten years post-vaccination against persistent infection was found for HPV type 31 (75.0%, 95% CI: 47.5-88.1%) only. Vaccine effectiveness estimates against cross-protective incident infections were statistically significant for the same HPV types with the addition of HPV type 45. In HAVANA2, a preliminary vaccine effectiveness of 88.6% (95% CI 61.5, 96.6) against incident genital infections related to HPV types 16/18 up to six years after vaccination was found (unpublished data). Preliminary vaccine effectiveness related to cross-protective HPV types 31/33/45 was 85.5% (95% CI 34.7, 96.8).

The quality and quantity of the immune response generated after receival of the bivalent vaccine according to a two-dose regimen is monitored within the HPV2D study [20]. High seroprevalences of 91% for HPV type 16 and 85% for HPV type 18 were observed up to 72 months after the first dose. Preliminary results regarding cross-protective HPV types showed seroconversion percentages of >88% for HPV types 31, 33, 45, 52 and 58 at 7 months after the first dose (i.e. one month after full vaccination). Up to 72 months after the first dose these seroprevalences ranged between 22% and 45%, with the lowest seroprevalence observed for HPV type 31 and the highest for HPV type 45. The geometric mean antibody concentrations of HPV types 31, 33, 45, 52 and 58 was lower compared with HPV types 16 and 18 at any timepoint, and, similar to HPV types 16 and 18, some waning of

geometric mean antibody levels for the cross-protective HPV types was observed.

By linking nation-wide registries on pathology and vaccination status, early effects of HPV-vaccination can be estimated on low-grade and high-grade squamous intraepithelial lesions or worse (LSIL and HSIL+) and hrHPV infection in young women up to 24 years of age who had a cervical smear taken before entry into the cervical cancer screening programme. For fully vaccinated women, reductions were seen for all outcomes when compared to unvaccinated women, with an adjusted odds ratio (OR) for hrHPV infections of 0.68 (95% CI 0.62, 0.74), for LSIL of 0.69 (95% CI 0.62, 0.77), and for HSIL+ of 0.44 (0.36, 0.54). Reductions were lower among incompletely vaccinated women [54](unpublished data).

Summary and conclusion HPV spectrum
Overall, scientific publications after 2019 show that the vaccines are effective in preventing cervical cancer and high risk cervical lesions, and are suggestive for protection against non-cervical HPV-related cancers. While all three vaccines are immunogenic up to several years after vaccination, vaccine responses after one dose are less immunogenic. Therefore, its possible effects on long-term effectiveness need to be established. There is evidence for cross-protection against some non-vaccine hrHPV types by use of the bivalent vaccine and the quadrivalent vaccine, although cross-protective effects of the quadrivalent vaccine have been studied less extensively. The observed cross-protective effects of the bivalent and quadrivalent vaccines were lower compared with the observed efficacy of the nonavalent vaccine of ≥95% against persistent infections, and cervical disease related to HPV types 31, 33, 45, 52, and 58 [49, 55]. Several vaccines that may induce an immune response against more than nine HPV-types are being developed and/or currently in the clinical phase of drug development [56]. The added value of these vaccines should be considered upon availability.

Low vaccination coverage in girls
To protect all girls and boys against HPV-related cancer, a gender-neutral HPV vaccination strategy will be implemented in the NIP from February 2022 onwards. The vaccine coverage among girls in The Netherlands has been relatively low since its introduction in the NIP, but increased in the past years. In 2018, the vaccine coverage was 46% for girls from birth cohort 2004, and increased in 2020 to 63% for girls from birth cohort 2006 [21]. The uptake of the gender neutral HPV vaccination programme will be monitored. Besides implementing gender neutral HPV vaccination, the Health Council advised to implement a lower age of vaccination. Implementation of both advices happens to fall within a period that Covid-19 vaccination was introduced for children, including children eligible for HPV-vaccination. Moreover, from 2022 onwards, informed consent is needed to register vaccination at the national level. This will introduce uncertainties in vaccination coverage estimates.

Several (qualitative) studies explored factors that may (indirectly) affect vaccination intention, vaccine uptake and vaccine coverage. A recent study has been performed in order to identity the factors that influence

the intention of parents to have their children and adolescents vaccinated against HPV [57]. Approximately 60-65% of the parents had a positive vaccination-intention and an automatic response is the most decisive factor as to whether parents intend to have their children vaccinated. Recommendations were as follows 1) exploit the naturalness of vaccination; 2) address parents of young children in regular communication; 3) motivate adolescents in a campaign context; and 4) stimulate the conversation in the family and among adolescents [58]. These recommendations are the foundation of the communication strategy for the gender-neutral HPV-vaccination, and are implemented in all communicational aspects, including the invitation letter, leaflet, campaign, and teaching materials for primary and secondary schools.

3.12.6 Conclusion and suggestions for the request for advice from the Health Council

In early 2022, the HPV vaccination programme was adapted. It now includes both girls and boys from nine to years of age.

Recently, the UK Joint Committee on Vaccines and Immunisations issued a positive advice for further reduced dose regimens, from a two- to a one-dose schedule for children aged below 15 years of age and from a three- to a two-dose schedule for individuals above that age. So far, these reduced schedules have not been registered by the European Medicines Agency.

HPV vaccines are effective in preventing cervical cancer and high-risk cervical lesions. When new vaccines against a wider spectrum of human papilloma viruses become available, their potential to aid in reaching the vaccination's goal should be considered.

3.12.7 References

1. Burchell, A.N., et al., *Chapter 6: Epidemiology and transmission dynamics of genital HPV infection.* Vaccine, 2006. **24 Suppl 3**: p. S3/52-61.
2. Chesson, H.W., et al., *The estimated lifetime probability of acquiring human papillomavirus in the United States.* Sex Transm Dis, 2014. **41**(11): p. 660-4.
3. International Agency for Research on Cancer, *Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100B: A Review of Human Carcinogens: Biological Agents.* 2012, International Agency for Research on Cancer: Lyon.
4. Schiffman, M., et al., *Human papillomavirus and cervical cancer.* Lancet, 2007. **370**(9590): p. 890-907.
5. de Martel, C., et al., *Worldwide burden of cancer attributable to HPV by site, country and HPV type.* Int J Cancer, 2017. **141**(4): p. 664-670.
6. Alemany, L., et al., *Role of Human Papillomavirus in Penile Carcinomas Worldwide.* European Urology, 2016. **69**(5): p. 953-961.
7. Alemany, L., et al., *Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide.* Int J Cancer, 2015. **136**(1): p. 98-107.
8. Alemany, L., et al., *Large contribution of human papillomavirus in vaginal neoplastic lesions: a worldwide study in 597 samples.* Eur J Cancer, 2014. **50**(16): p. 2846-54.

9. de Sanjosé, S., et al., *Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva.* Eur J Cancer, 2013. **49**(16): p. 3450-61.

10. Rietbergen, M.M., et al., *Epidemiologic associations of HPV-positive oropharyngeal cancer and (pre)cancerous cervical lesions.* Int J Cancer, 2018. **143**(2): p. 283-288.

11. Mehanna, H., et al., *Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region.* Head Neck, 2013. **35**(5): p. 747-55.

12. Ndiaye, C., et al., *HPV DNA, E6/E7 mRNA, and p16^{INK4a} detection in head and neck cancers: a systematic review and meta-analysis.* The Lancet Oncology, 2014. **15**(12): p. 1319-1331.

13. *Nederlandse Kankerregistratie (NKR), IKNL. Verkregen via iknl.nl/nkr-cijfers.*

14. Centraal bureau voor de statistiek, *StatLine*.

15. Gezondheidsraad, *Vaccinatie tegen HPV*. 2019: Den Haag.

16. European Medicines Agency, *Cervarix human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)*, in *Summary of product characteristics*.

17. European Medicines Agency, *Gardasil human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)*, in *Summary of product characteristics*.

18. European Medicines Agency, *Gardasil 9 International non-proprietary name: human papillomavrius 9-valent vaccine (RECOMBINANT, ADSORBED)*, in *Assessment report*.

19. Strategic Advisory Group of Experts (SAGE) on Immunization, *Working Group onpotential contribution of Human Papillomavirus (HPV) vaccines and immunization towards cervical cancer elimination*. 2019.

20. National Institute for Public Health and the Environment, *The National Immunisation Programme in the Netherlands. Surveillance and developmentes in 2020-2021*. 2021.

21. Rijksinsituut voor Volksgezondheid en Milieu, *Vaccinatiegraad en jaarverslag. Rijksvaccinatieprogramma Nederland 2020*. 2021.

22. WHO, *Cervical Cancer Elimination Initiative [Available from: https://www.who.int/initiatives/cervical-cancer-elimination-initiative]*. 2020.

23. Whitworth, H.S., et al., *Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to no vaccination or standard three and two-dose vaccination regimens: A systematic review of evidence from clinical trials.* Vaccine, 2020. **38**(6): p. 1302-1314.

24. Pasmans, H., et al., *Long-term HPV-specific immune response after one versus two and three doses of bivalent HPV vaccination in Dutch girls.* Vaccine, 2019. **37**(49): p. 7280-7288.

25. Kreimer, A.R., et al., *Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial.* J Natl Cancer Inst, 2020. **112**(10): p. 1038-1046.

26. Sankaranarayanan, R., et al., *Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study.* Lancet Oncol, 2016. **17**(1): p. 67-77.

27.   Toh, Z.Q., et al., *Sustained Antibody Responses 6 Years Following 1, 2, or 3 Doses of Quadrivalent Human Papillomavirus (HPV) Vaccine in Adolescent Fijian Girls, and Subsequent Responses to a Single Dose of Bivalent HPV Vaccine: A Prospective Cohort Study.* Clin Infect Dis, 2017. **64**(7): p. 852-859.

28.   Basu, P., et al., *Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study.* Lancet Oncol, 2021. **22**(11): p. 1518-1529.

29.   Verdoodt, F., C. Dehlendorff, and S.K. Kjaer, *Dose-related Effectiveness of Quadrivalent Human Papillomavirus Vaccine Against Cervical Intraepithelial Neoplasia: A Danish Nationwide Cohort Study.* Clin Infect Dis, 2020. **70**(4): p. 608-614.

30.   Batmunkh, T., et al., *A single dose of quadrivalent human papillomavirus (HPV) vaccine is immunogenic and reduces HPV detection rates in young women in Mongolia, six years after vaccination.* Vaccine, 2020. **38**(27): p. 4316-4324.

31.   Secor, A.M., et al., *Immunogenicity of Alternative Dosing Schedules for HPV Vaccines among Adolescent Girls and Young Women: A Systematic Review and Meta-Analysis.* Vaccines (Basel), 2020. **8**(4).

32.   Joint Committee on Vaccination and Immunisation, *JCVI interim advice on a one-dose schedule for the routine HPV immunisation programme*. 2022, Joint Committee on Vaccination and Immunisation,.

33.   Joint Committee on Vaccination and Immunisation, *Joint Committee on Vaccination and Immunisation: statement on the delivery of the HPV vaccine*. 2020.

34.   Baisley, K.J., et al., *A dose-reduction HPV vaccine immunobridging trial of two HPV vaccines among adolescent girls in Tanzania (the DoRIS trial) - Study protocol for a randomised controlled trial.* Contemp Clin Trials, 2021. **101**: p. 106266.

35.   Barnabas, R.V., et al., *Single-dose HPV vaccination efficacy among adolescent girls and young women in Kenya (the KEN SHE Study): study protocol for a randomized controlled trial.* Trials, 2021. **22**(1): p. 661.

36.   Barnabas, R.V., et al., *Efficacy of single-dose HPV vaccination among young African women.* Preprint by Research Square, 2021.

37.   Zeng, Y., et al., *A prospective, single-arm, open-label, non-randomized, phase IIa trial of a nonavalent prophylactic HPV vaccine to assess immunogenicity of a prime and deferred-booster dosing schedule among 9-11 year-old girls and boys - clinical protocol.* BMC Cancer, 2019. **19**(1): p. 290.

38.   Markowitz, L.E., et al., *Human papillomavirus vaccine effectiveness by number of doses: Systematic review of data from national immunization programs.* Vaccine, 2018. **36**(32 Pt A): p. 4806-4815.

39.   Hampson, I.N., A.W. Oliver, and L. Hampson, *Potential Effects of Human Papillomavirus Type Substitution, Superinfection Exclusion and Latency on the Efficacy of the Current L1 Prophylactic Vaccines.* Viruses, 2020. **13**(1).

40. Walboomers, J.M., et al., *Human papillomavirus is a necessary cause of invasive cervical cancer worldwide.* J Pathol, 1999. **189**(1): p. 12-9.

41. Rietbergen, M.M., et al., *Epidemiologic associations of HPV-positive oropharyngeal cancer and (pre)cancerous cervical lesions.* International Journal of Cancer, 2018. **143**(2): p. 283-288.

42. Falcaro, M., et al., *The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study.* The Lancet, 2021.

43. Luostarinen, T., et al., *Vaccination protects against invasive HPV-associated cancers.* Int J Cancer, 2018. **142**(10): p. 2186-2187.

44. Kjaer, S.K., et al., *Long-term effectiveness of the nine-valent human papillomavirus vaccine in Scandinavian women: interim analysis after 8 years of follow-up.* Hum Vaccin Immunother, 2021. **17**(4): p. 943-949.

45. Olsson, S.E., et al., *Long-term immunogenicity, effectiveness, and safety of nine-valent human papillomavirus vaccine in girls and boys 9 to 15 years of age: Interim analysis after 8 years of follow-up.* Papillomavirus Res, 2020. **10**: p. 100203.

46. Giuliano, A.R., et al., *Nine-valent HPV vaccine efficacy against related diseases and definitive therapy: comparison with historic placebo population.* Gynecol Oncol, 2019. **154**(1): p. 110-117.

47. Schwarz, T.F., et al., *A ten-year study of immunogenicity and safety of the AS04-HPV-16/18 vaccine in adolescent girls aged 10-14 years.* Hum Vaccin Immunother, 2019. **15**(7-8): p. 1970-1979.

48. Ferris, D.G., et al., *4-Valent Human Papillomavirus (4vHPV) Vaccine in Preadolescents and Adolescents After 10 Years.* Pediatrics, 2017. **140**(6).

49. Brown, D.R., et al., *Systematic literature review of cross-protective effect of HPV vaccines based on data from randomized clinical trials and real-world evidence.* Vaccine, 2021. **39**(16): p. 2224-2236.

50. Beyer, W.E.P. and A. Osterhaus, *Bivalent AS04-adjuvanted HPV vaccine provides optimal cancer prevention for HPV types not included in the vaccine.* Vaccine, 2020. **38**(47): p. 7414-7416.

51. Stanley, M., et al., *Systematic literature review of neutralizing antibody immune responses to non-vaccine targeted high-risk HPV types induced by the bivalent and the quadrivalent vaccines.* Vaccine, 2021. **39**(16): p. 2214-2223.

52. Hoes, J., et al., *Persisting Antibody Response 9 Years After Bivalent Human Papillomavirus (HPV) Vaccination in a Cohort of Dutch Women: Immune Response and the Relation to Genital HPV Infections.* J Infect Dis, 2020. **221**(11): p. 1884-1894.

53. Hoes, J., et al., *Vaccine effectiveness following routine immunization with bivalent HPV vaccine: Protection against incident genital HPV infections from a reduced-dosing schedule.* J Infect Dis, 2021.

54. National Institute for Public Health and the Environment, *The National Immunisation Programme in the Netherlands. Surveillance and developments in 2019-2020*. 2020.

55. Huh, W.K., et al., *Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial.* Lancet, 2017. **390**(10108): p. 2143-2159.
56. U.S. National Library of Medicine. *ClinicalTrials*. 2021 [cited 2021 22 Dec]; Available from: ClinicalTrials.gov.
57. MarketResponse, *Gedragsonderzoek HPV-vaccinatie*. 2021.
58. van den Wijngaard, R. and N. van Gaalen, *Mensen activeren om zichzelf of hun kinderen te laten vaccineren tegen HPV.* 2021.

4 General discussion

In this chapter of the document the perspective will be broadened to the level of the NIP. Overall conclusions will be drawn. Issues transcending the bounds of specific vaccinations will also be discussed in this section, e.g. conflicting preferences of timing for components of combination vaccines. The findings of the previous chapters will be summarised in an infographic way with the current and ideal immunisation schedules for the various individual vaccinations with room for manoeuvre. The infographic may facilitate discussion of potential conflicting considerations in the Health Council.

4.1 Overall conclusions

The NIP consists of a diverse range of vaccinations
The NIP consists of a diverse range of vaccinations with different overall goal and strategies (Table 4.1). The three main classes of goal and strategy are: 1) To protect as many vulnerable persons as possible against serious disease, 2) To foster and maintain indirect protection, and 3) Elimination or eradication. A complicating factor is that the DTaP-IPV-Hib-HepB, dTap-IPV and MMR combination vaccines comprise vaccinations of these different classes.

The diverse vaccinations of the NIP present with sometimes conflicting considerations
Because of the different goals and strategies of the diverse vaccinations in combination vaccines they may present with sometimes conflicting considerations. These considerations are explored in more detail in paragraph 4.2.

There is not one ideal immunisation schedule; it may be unavoidable to compromise
There is not one ideal immunisation schedule. It may be sometimes unavoidable to compromise. Ideal immunisation schedules for the various individual vaccinations with room for manoeuvre are given in Figure 4.1. No effort was made to solve existing dilemma's and conflicting considerations at this point. Instead these are presented graphically for discussion by the Health Council.

Figure 1 NIP vaccinations: goal and strategy, critical, current and target coverages

Goal and strategy	Target disease	Basic reproductive rate R_0	Critical vaccination coverage for elimination of infection in a homogeneously mixing population (estimated as $(R_0-1)/R_0 \times 100\%$)	Current vaccination coverage in the Netherlands (percentage, 2021)[19]	Target vaccination coverage (percentage) for the Netherlands based on WHO guidance[20, 21]	Remarks and assessment
Protect as many vulnerable persons as possible against serious disease						
	Diphtheria	5-7[1, 2]	80-86	93.1	95 (basic series)	Complex infectious cycle, critical vaccination coverage is an approximation only
	Pertussis	5-17[1,2,3]	Not applicable	93.1	95 (basic series)	Limited herd protection and duration of immunity, elimination not possible by childhood vaccination
	Tetanus	Not applicable[4]	Not applicable	93.1	95 (basic series)	Not transmissible between people
	Cancer caused by human papillomavirus infection	2-5[5,6]	50-80 (girls and boys), 90-95 (girls only)	63.1 (girls)	90 (girls 15 years of age)	As an STD elimination is difficult, applies to vaccine types only
Foster and maintain indirect protection (of various degrees possible)						
	Invasive disease by *Haemophilus influenzae* type b infection	1.1-3.3[7,8]	Not applicable	93.8	Not defined	Immunity protects against disease but less against carriage. Herd protection is incomplete and bacterium remains in circulation
	Mumps	4-14[1,2,9]	75-88	93.6	>80 (two doses)	Immunity wanes, but serious complications

Goal and strategy	Target disease	Basic reproductive rate R_0	Critical vaccination coverage for elimination of infection in a homogeneously mixing population (estimated as $(R_0-1)/R_0 \times 100\%$)	Current vaccination coverage in the Netherlands (percentage, 2021)[19]	Target vaccination coverage (percentage) for the Netherlands based on WHO guidance[20, 21]	Remarks and assessment
						are rare with reinfection among vaccinated persons
	Invasive pneumococcal disease	1-5[10,11]	Not applicable	93.3	Not defined	Elimination of vaccine types only, replacement by non-vaccine types
	Invasive meningococcal disease	1-2[12]	Not applicable	93.3	Not defined	Contagion is from nasopharyngeal carriage among adolescents mainly
Elimination or eradication (international)						
	Poliomyelitis	2-4[2,13]	50-75	93.1	'every last child'	Worldwide eradication is within reach
	Measles	12-23[1,2,14,15]	92-96	93.6	95 (first and second dose)	Elimination is possible, but dependent on international collaboration
	Rubella	4-8[1,2,16]	75-88	93.6	>85-90 (one dose)	Elimination is possible
	Hepatitis B	1.5-4[17,18]	33-75	93.0	95 (three doses)	As a chronic infection and STD critical vaccination coverage is an approximation only. Elimination is difficult and will take many years

STD = sexually transmissible disease

[1] Anderson, R.M., T.D. Hollingsworth, and D.J. Nokes, *Mathematical models of transmission and control*. In *Oxford Textbook of Public Health*. Detels R, et al, editors. Oxford: Oxford University Press; 2009.

[2] Vynnycky, E. and R.G. White, *An introduction to infectious disease modelling*. New York: Oxford University Press; 2010.

[3] Kretzschmar, M., P.F. Teunis and R.G. Pebody, *Incidence and reproduction numbers of pertussis: estimates from serological and social contact data in five European countries*. PLoS Med, 2010. 7(6): p. e1000291.

[4] World Health Organization, *Tetanus vaccines: WHO position paper - February 2017*. Weekly epidemiological record, 2017. 92(6): p. 53-76.

[5] Bogaards, J.A., et al., *Long-term impact of human papillomavirus vaccination on infection rates, cervical abnormalities, and cancer incidence*. Epidemiology, 2011. 22(4): p. 505-15.

[6] Brisson, M., et al., *Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models*. Lancet Public Health, 2016. 1(1): p. e8-e17.

[7] Charania, N.A. and S.M. Moghadas, *Modelling the effects of booster dose vaccination schedules and recommendations for public health immunization programs: the case of Haemophilus influenzae serotype b*. BMC Public Health, 2017. 17(1): p. 705.

[8] Coen, P.G., et al., *Mathematical models of Haemophilus influenzae type b*. Epidemiol Infect, 1998. 120(3): p. 281-95.

[9] Anderson, R.M., J.A. Crombie, and B.T. Grenfell, *The epidemiology of mumps in the UK: a preliminary study of virus transmission, herd immunity and the potential impact of immunization*. Epidemiol Infect, 1987. 99(1): p. 65-84.

[10] Hoti, F., et al., *Outbreaks of Streptococcus pneumoniae carriage in day care cohorts in Finland - implications for elimination of transmission*. BMC Infect Dis, 2009. 9: p. 102.

[11] Gjini, E., *Geographic variation in pneumococcal vaccine efficacy estimated from dynamic modeling of epidemiological data post-PCV7*. Sci Rep, 2017. 7(1): p. 3049.

[12] Trotter, C.L. and M.C. Maiden, *Meningococcal vaccines and herd immunity: lessons learned from serogroup C conjugate vaccination programs*. Expert Rev Vaccines, 2009. 8(7): p. 851-61.

[13] Fine, P.E. and I.A. Carneiro, *Transmissibility and persistence of oral polio vaccine viruses: implications for the global poliomyelitis eradication initiative*. Am J Epidemiol, 1999. 150(10): p. 1001-21.

[14] Guerra, F.M., et al., *The basic reproduction number (R0) of measles: a systematic review*. Lancet Infect Dis, 2017. 17(12): p. e420-e428.

[15] Wallinga, J., P. Teunis, and M. Kretzschmar, *Reconstruction of measles dynamics in a vaccinated population*. Vaccine, 2003. 21(19-20): p. 2643-50.

[16] Edmunds, W.J., et al., *Modelling rubella in Europe*. Epidemiol Infect, 2000. 125(3): p. 617-34.

[17] Kretzschmar, M., et al., *Vaccination against hepatitis B in low endemic countries*. Epidemiol Infect, 2002. 128(2): p. 229-44.

[18] Mann, J. and M. Roberts, *Modelling the epidemiology of hepatitis B in New Zealand*. J Theor Biol, 2011. 269(1): p. 266-72.

[19] At two years of age, except for HPV where it is at 14 years of age

[20] See *European Vaccination Action Plan* (https://www.euro.who.int/__data/assets/pdf_file/0007/255679/WHO_EVAP_UK_v30_WEBx.pdf) and WHO position papers (https://www.who.int/teams/immunization-vaccines-and-biologics/policies/position-papers)

[21] World Health Organization, *Global strategy to accelerate the elimination of cervical cancer as a public health problem.*

4.2 The diverse vaccinations of the NIP present with sometimes conflicting considerations

Is the timing of the combined vaccination against diphtheria, tetanus, pertussis, polio, hepatitis B and *Haemophilus influenzae* type b (DTaP-IPV-Hib-HepB) optimal or at least acceptable?
From the perspective of vaccination against diphtheria
As substantiated in Chapter 3.1, the protection against diphtheria induced by vaccination is long-lasting, even though the precise determinants for protection are not known. Antibody levels against diphtheria do decline during adulthood, but the decline is not reflected by a rise in cases. There is no such feeling that the current immunisation schedule includes too many immunisations. The current booster at four years of age, however, may be redundant.

From the perspective of vaccination against tetanus
Protection against tetanus induced by vaccination is long-lasting, even though the precise determinants for protection are not known (Chapter 3.3). The current vaccination schedule may include more and more frequent immunisations against tetanus than necessary. Thus, the number of immunisations may be reduced and the intervals between doses may be increased. The use of tetanus antigen as a carrier protein for other vaccines most likely adds to the immunity against tetanus and a relevant question is whether and how such use could be taken into account.

From the perspective of vaccination against pertussis
The current immunisation schedule, using acellular pertussis vaccines, with a first booster at 11 month age and a second booster at 4 years of age results in high antibody levels at preschool age, but also in high T-cell cytokine levels potentially associated with adverse events and the presence of more terminally differentiated CD4+ T-cells. The occurrence of adverse events following repeated aP containing booster doses is probably also impacted by antigen dose and timing of the vaccination. Longer intervals between aP vaccinations for toddlers and preschool children seem appropriate. With the aP vaccines currently available such a schedule could comprise primary vaccinations at 3 and 5 months of age and a first booster at 12–15 or even 18 months and a low dose booster at the age of 5–6 years (Chapter 3.2).

From the perspective of vaccination against polio
A series of three infant doses of IPV vaccine is sufficient for protection against paralytic disease. There is no evidence that protective immunity against paralytic disease wanes over time. The timing of further booster doses is flexible. A primary series of two doses and one booster dose confers good and long-lasting protection against paralytic disease. The current number of 5 IPV doses is probably higher than necessary and may be reduced to a 0 to 18 years schedule including 4 doses instead of the current 0-9 years schedule (Chapter 3.4).

From the perspective of vaccination against hepatitis B
Vaccination against hepatitis B is complicated, since it should cover both primary prevention for most children and secondary prevention for children of mothers with chronic HBV infection (Chapter 3.5).
A routine vaccination schedule for primary prevention of hepatitis B includes three doses. The interval between doses is a minimal four weeks but this can be longer. The schedule is therefore flexible and in the routine schedule the first dose can be given between 6 weeks and 3 months of age, the second dose at least four weeks later and the last dose after an interval of at least six months. The currently used schedule with doses at 3, 5, and 11 months meets these requirements. Children of mothers with chronic HBV infection constitute a special group. These children need secondary prevention in order to avoid becoming chronically infected. The ideal vaccination schedule for this group of children, as recommended by WHO, should include doses at birth, one and six months of age. In the Dutch NIP, however, these children receive two early doses of hepatitis B vaccine, at birth (*stand alone*) and at two months of age (as DTaP-IPV-Hib-HepB combination vaccine). From thereon the immunisation schedule for children of mothers with chronic HBV infection currently follows the routine schedule with doses at 3, 5 and 11 months of age (as combination vaccine).
Thus, in the current Dutch schedule children of mothers with chronic HBV infection receive a DtaP-IPVHepBHib combination vaccine at two month of age, whereas in most cases a hepatitis B *stand alone* vaccine would be sufficient (only those needing extra protection against pertussis would be expected to benefit). By following the routine schedule at 3, 5 and 11 month of age, they also receive more doses of hepatitis B vaccine than necessary. Deviating from the routine schedule, however, might be prone to error.

From the perspective of vaccination against Haemophilus influenzae type b
In the current immunisation schedule against *Haemophilus influenzae* type b with doses at (2,) 3, 5, and 11 months of age, the 11-months booster comes quite early (Chapter 3.6). Available evidence suggests administration of the booster a few months later could be more effective.

Concurrent and conflicting considerations
Postponement of the 11-months DTaP-IPV-Hib-HepB booster: good for vaccination against pertussis and Hib?
For all diseases targeted by the DTaP-IPV-Hib-HepB combination vaccine the primary series at (2), 3 and 5 months need to be maintained. The booster, now at 11 months, may be better postponed a few months for the purpose of vaccination against invasive disease by infection with *Haemophilus influenzae* type b, a change that could also be favourable for vaccination against pertussis using the current acellular vaccines. For vaccination against diphtheria, tetanus, and polio, postponement of the 11-months booster by a few months might induce slightly better immunity and at least is not problematic . The same probably applies to vaccination against hepatitis B, even for the group of children born to mothers with chronic infection, for whom optimal protection is so important.

Postpone or skip the 4-year dtap-IPV booster?
For vaccination against pertussis, the 4-year booster may best be postponed until 5-6 years, but for protection against tetanus and polio it probably is redundant and could as well be skipped. For diphtheria, too, it may be redundant when a better spread over the entire NIP age band (0-18 year) could be realized.

Postpone the 9-year dt-IPV booster, but to what age?
The age of administration of the dt-IPV booster, currently at nine years, is not critical. Depending on whether or not the earlier booster is maintained and at what age, it could probably best be postponed till late in adolescence to increase the span of the protection provided by the NIP.

Is the timing of the combined vaccination against measles, mumps and rubella optimal or at least acceptable?
From the perspective of vaccination against measles
The timing of the current immunisation schedule (doses at 14 months and 9 years of age) is acceptable for protection against measles (Chapter 3.10). The second dose of measles vaccine, now administered at nine years of age, is primarily given as a second chance to induce immunity in children who did not respond to the first dose. Therefore, it could be considered to advance the second dose and thus reduce the number of susceptible children during an outbreak. Thus, an overall better protection of toddlers and young children could be achieved. Administering the second of MMR vaccine dose at a younger age might also improve vaccination uptake, as data show that the uptake of the DTP booster at 4 years is 2-5% higher than the uptake of MMR2 at 9 years.

From the perspective of vaccination against mumps
The timing of the current schedule is also acceptable for protection against mumps (Chapter 3.9). After a first dose, effective immunity against mumps infection is established, and although it wanes over time, it rarely leads to reinfection before the age of the booster dose at nine years of age. The second dose boosts immunity, adding about ten years of protective immunity, roughly covering the period throughout adolescence, but susceptibility increases in young adults. Therefore, the question arises whether postponing the second dose for example to the age of 12-14 years could lengthen the period of protective immunity. However, there is limited data from other countries to support such a change.

From the perspective of vaccination against rubella
The current immunisation schedule is very effective for the prevention of rubella and the congenital rubella syndrome. The timing of the two doses is not critical, but it is important that the second dose is administered before childbearing age. Similarly as for measles, advancing the second dose could lead to increased uptake of vaccination against rubella.

Concurrent and conflicting considerations

Advancing the age at which MMR2 is given
Administering the second dose of MMR vaccine before 9 years would be advantageous for protection against measles, but may be disadvantageous for the protection against mumps. Although it will most likely result in decreased susceptibility to mumps virus infection at younger age, it will most likely lead to a larger susceptible group at the adolescent/young adult age. Experiences in countries with different vaccination schedules may inform the issue. A review of literature available on PubMed published between 2010 and 2021 identified a limited number of outbreaks that occurred mainly among twice vaccinated adolescents aged 13-18 years, while the vast majority of reported outbreaks occurred among twice vaccinated young adults aged 18-25 years. Outbreaks that were reported (mainly) among children aged 13-18 years were associated with conditions of crowding and intense contact, as most outbreaks in that age group, and occurred in countries in which the second dose of MMR was administered at 6 years of age or younger.
Therefore, administering the second vaccination of the MMR vaccine at a younger age than the current vaccination schedule will most likely result in increased susceptibility to mumps among younger individuals (e.g. children 13-18 years of age), but infections/outbreaks will most likely only occur among conditions of crowding and intense contact. In conclusion, advancing the second dose of MMR vaccine might be disadvantageous for the protection against mumps.

Postponing the second dose at which MMR2 is given
Administering the second dose of MMR vaccine at a later age than currently might be advantageous for protection against mumps. However, evidence to support such a change is very limited. Also, it is probably disadvantageous for protection against measles and rubella that potentially carry a larger burden of severe disease.

4.3   There is not one ideal immunisation schedule; compromise may be unavoidable

There is not one ideal immunisation schedule and it may be sometimes unavoidable to compromise. Current and ideal immunisation schedules for the various individual vaccinations are given in Figure 4.1, with room for manoeuvre. No effort was made to solve existing dilemma's and conflicting considerations at this point. Instead these are presented graphically for discussion by the Health Council.

Figure 2 Current and optimal NIP vaccination schedules, room for manoeuvre, The Netherland
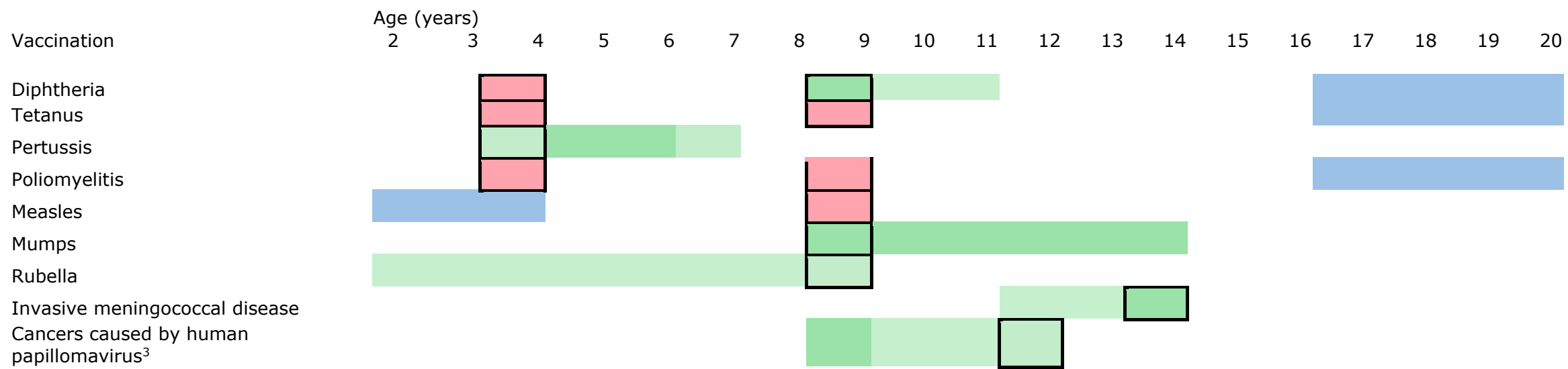
NIP vaccination schedule for infants and children < 2y
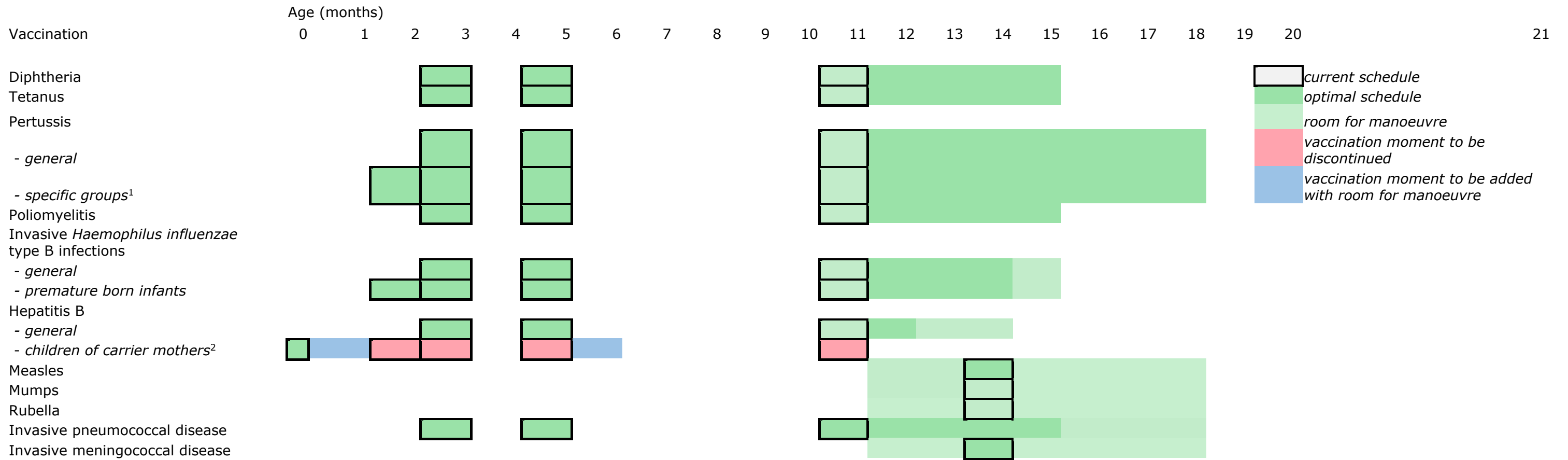
[1] premature born infants, infants born to mothers not vaccinated during pregnancy or to mothers with immune disease

[2] optimal schedule to be discussed in conjunction with healthcare factors and logistics

NIP vaccination schedule for children 2-18y

[3] girls only, 12 and 12.5 years of age; from 2022 boys will be included and age at vaccination will be 9 years

Combination vaccines used for current schedule

Age (month)	Combination vaccine
2	DTaP-IPVHepBHib
3	DTaP-IPVHepBHib
5	DTaP-IPVHepBHib
11	DTaP-IPVHepBHib
14	MMR

Age (years)	
4	dtap-IPV
9	dt-IPV MMR

Glossary of terms

Innate immunity	Inborn general (non-specific) and fast immune responses as a first line of defence for the first critical hours and days of exposure to a new pathogen
Acquired immunity	Specific immunity that takes over if the innate immune system is not able to destroy the pathogen. By specifically identifying and targeting the type of germ causing the infection it is more accurate but also slower to respond than the innate immunity. The innate and acquired immune systems work closely together
Vaccine-induced immunity	Specific immunity induced by vaccination
Maternal immunity	Protection of the newborn in the months following birth against disease/infection through maternal antibodies transmitted to the fetus via the placenta
Basic reproduction number R_0	Measure for the infectiousness of a pathogen: average number of individuals infected by a single infected individual in a susceptible population
Outbreak	Transient upsurge of infections/disease in a subset of the population
Epidemic	Largescale spread of a pathogen, that without active control measures may result in endemic circulation
Endemic spread	Uninterrupted circulation of a pathogen in a population
Eradication	Worldwide absence of circulation of a pathogen
Elimination	Absence of circulation of a pathogen/an infectious disease. WHO definition: no pathogen/disease detected in a country (or region) for at least 12 months with standardised surveillance
Indirect protection	Reduced occurrence of disease/infection among non-vaccinated individuals because of reduced circulation of a disease or pathogen as a result of partial vaccination of a population
Herd immunity	Protection of a whole population through immunisation of a critical proportion of individuals such that pathogen circulation becomes impossible
Herd immunity threshold	Minimum proportion of immune individuals in a homogeneously mixing population needed to reach elimination of a pathogen
Critical vaccination level	Minimum vaccination coverage corresponding to the herd immunity threshold