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

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*Optimisation of the vaccination policy*

RIVM Letter Report 215121002/2012
M.A.E. Conyn | N.A.T. van der Maas | F.M. Mooi

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# Colofon



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# Abstract

**Control of whooping cough in the Netherlands:**
vaccination at the end of pregnancy

Immunisation of women at the end of pregnancy is a feasible and effective method to prevent disease and death from whooping cough (pertussis) in newborn children. Researchers attached to the *RIVM* have assessed various possible vaccination strategies to reduce the incidence of pertussis, especially to reduce the risk for newborns. These are too young to be immunised themselves, but there are possibilities to protect them indirectly.

Since the mid-nineties of the previous century, there has been an increase in incidence of pertussis despite immunisation in the National Immunisation Programme. This rise is most notable in very young children (younger than 3-5 months, too young to be immunised) and children between the age of 6 and 19. Furthermore, adults increasingly present pertussis, albeit in a less typical form. They are often the source of infection of infants. Those children in particular may have a severe course of pertussis. This leads to 50-100 hospitalisations per year and incidentally, death. The Netherlands are not alone in such, many countries have demonstrated this development.

Various possible vaccination strategies to improve the protection of young infants from pertussis have been assessed. This entails e.g. early vaccination of the infant (right after birth), vaccination of the prospective mother at the end of pregnancy, vaccination of mothers or fathers after birth, vaccination of people in close proximity with babies due to their profession (health- or childcare), vaccination of women with a known wish to become pregnant or an additional booster administered to children and adolescents.
For each scenario, the following aspects have been assessed: 1. Safety, 2. Immunogenicity and effectiveness, 3. Cost-effectiveness, 4. Feasibility and operational aspects and 5. Known unknowns. The authors considered immunisation of mothers at the end of pregnancy as a feasible and effective method with a potential high impact on incidence and mortality in newborns.

Keywords:
Whooping cough, optimisation, vaccination policy, scenario's

# Rapport in het kort

**Optimalisatie van de bestrijding van kinkhoest: vaccinatie van zwangere vrouwen**

Vaccinatie van vrouwen op het eind van de zwangerschap is een haalbare en doelgerichte benadering om ziekte en sterfte door kinkhoest bij pasgeborenen te voorkomen.
Onderzoekers van het RIVM beoordeelden verschillende mogelijke vaccinatiescenario's om kinkhoest terug te dringen, met name om de risico's voor pasgeborenen te beperken. Bij hen treedt de meest ernstige ziekte en soms ook sterfte door kinkhoest op. Zij zijn nog te jong om zelf gevaccineerd te zijn maar er zijn mogelijkheden om hen indirect te beschermen.

Sinds midden jaren negentig van de vorige eeuw is er ondanks de vaccinatie tegen kinkhoest in het Rijksvaccinatieprogramma een toename van het aantal gevallen van kinkhoest. De toename wordt vooral gezien bij heel jonge kinderen (jonger dan 3-5 maanden, te jong om gevaccineerd te zijn) en kinderen van 6 tot 19 jaar. Ook bij volwassenen komt steeds vaker kinkhoest voor, zij het vaak in een minder typische vorm. Vaak zijn zij de bron van besmetting van zuigelingen. Juist bij deze heel jonge kinderen kan kinkhoest ernstig verlopen. Het leidt tot 50 à 100 ziekenhuisopnames per jaar en in een enkel geval zelfs tot overlijden. Niet alleen in Nederland, maar in veel landen doet deze ontwikkeling zich voor.

Diverse mogelijke vaccinatiescenario’s om de bescherming van jonge zuigelingen tegen kinkhoest te verbeteren zijn beoordeeld. Het gaat om bijvoorbeeld vroegere vaccinatie van de zuigeling, vlak na de geboorte, vaccinatie van de aanstaande moeder op het einde van de zwangerschap, vaccinatie van moeders of ook vaders na de geboorte van een baby en vaccinatie van mensen die professioneel in contact komen met de baby (in de zorg of kinderopvang), of vaccinatie van vrouwen met kinderwens voordat er zwangerschap optreedt, of een extra vaccinatie van kinderen en adolescenten.
Per scenario is gekeken naar 1. veiligheid, 2. werkzaamheid en effectiviteit, 3. doelmatigheid, 4. haalbaarheid en operationele aspecten, en 5. ‘bekende onbekende zaken’.
De auteurs zagen vaccinatie van moeders op het einde van de zwangerschap als een haalbare en doelgerichte benadering met potentieel hoge impact op ziekte en sterfte bij pasgeborenen.

Deze verkenning wordt ingebracht in de beraadslagingen van de Gezondheidsraad over kinkhoestvaccinatie.

Trefwoorden:
Kinkhoest, optimalisatie, vaccinatiescenario's

# Contents


# CONTROL OF WHOOPING COUGH IN THE NETHERLANDS: OPTIMISATION OF THE VACCINATION POLICY

## 1 Introduction

The inadequate control of whooping cough, which became obvious in ongoing surveillance, is worrying and induced us to consider possible scenarios to improve the prevention by vaccination. In the Netherlands, it is the Health Council's task to counsel the minister of health on the National Immunisation Programme (NIP). In this document, we aim to bring together information which is relevant for advising on pertussis control using our experience with epidemiological and pathogen surveillance, research on safety and immunological mechanisms, mathematical modelling and cost-effectiveness analysis. Thus, this document may be used by the NIP committee of the Health Council as a point of departure in its advising on improving pertussis control by vaccination, as well as for a debate with other interested parties, such as ECDC. (1)

The recent increase of pertussis, with a high incidence among a broadening range of age groups, is particularly alarming because it affects neonates who are too young to be vaccinated and who are most endangered by pertussis (2 deaths in newborns due to pertussis in 2012). The primary objective of pertussis vaccination is to prevent pertussis in this vulnerable age group. This could be achieved by reducing the force of infection in the population in general or -more efficiently- by increasing indirect protection by vaccinating close contacts of newborns only. Therefore -while comparing several vaccination scenarios- our focus is on the protection of newborns, either directly or indirectly, not per se on the decrease of the force of infection by revaccinating huge groups. Other ways of preventing or mitigating pertussis in newborns, such as chemoprophylaxis when whooping cough occurs close to a neonate or a pregnant woman expected to deliver soon, are not part of this paper.

Several scenarios will be discussed; these are evaluated according to 1. 'Safety', 2. 'Immunogenicity and effectiveness', 3. 'Cost-effectiveness' and 4. 'Feasibility and operational aspects' and in 5. 'Known unknowns', we indicate what data are lacking and could still be collected.

Further, a paragraph is included on the need for improved vaccines, which is largely based on our insight in whooping cough epidemiology and *B.pertussis* (molecular) biology and on scientific reports from other groups. At the moment it appears that improved vaccines are not to be expected within reasonable time. (2) The addendum presents an overview of the pertussis antigen containing vaccines with a market authorisation in the Netherlands and the vaccination schedules applied in different European countries.

## 2 Situation in the Netherlands

Notwithstanding a number of measures taken to improve the effectiveness of pertussis vaccination since its increase at the end of the nineties of the previous century, pertussis is still not under control. Changes in the vaccination policy in the Netherlands in the course of time were:

- November 1997: increase of the concentration of *B.pertussis* cells from 4 to 7 IOU (international opacity units) in the DTP-IPV vaccine produced by the Netherlands Vaccine Institute (NVI), at the time part of the National Institute of Public Health and the Environment (RIVM);
- January 1, 1999: accelerated immunisation schedule, with the first dose DTP-IPV and Hib at the age of 2 instead of 3 months;
- November 2001: introduction of a booster dose for 4-year-old children (born from January 1, 1998 onwards), initially with a separate acellular pertussis vaccine, in addition to the regular DT-IPV vaccine, but since the third quarter of 2006 with a DTaP-IPV combination vaccine;
- January 1, 2005: replacement of the pertussis component in the $DT_{w \rightarrow a}P$-IPV-Hib-vaccine for infants (acellular instead of cellular, 'whole cell' vaccine), for birth cohort from February 1, 2004, onwards.

Figure 1 shows the different schedules and vaccines used in the Netherlands for birth cohorts 1991 onwards.

<table>
<tr><td>cohort</td><td>1991-1996</td><td>1997</td><td>1998</td><td>1999</td><td>2000</td><td>2001</td><td>2002</td><td>2003</td><td>2004[a]</td><td>2005</td><td>2006</td><td>2007</td></tr>
<tr><td>Infant<br>4 doses</td><td>whole-cell vaccine<br>DT-wP-IPV-Hib</td><td colspan="2">whole-cell vaccine<br>DT-wP-IPV-Hib, increased IOU/ml</td><td colspan="5">whole-cell vaccine<br>DT-wP-IPV-Hib, increased IOU/ml, accelerated schedule</td><td colspan="3">acellular vaccine<br>DTaP-IPV-Hib(+hepB)</td></tr>
<tr><td>vaccine</td><td colspan="9">RIVM-DKTP-Hib</td><td>Infanrix-IPV-Hib</td><td colspan="2">Pediacel (or InfanrixHexa)</td></tr>
<tr><td>4<br>years<br>booster</td><td>No pertussis<br>DT-IPV</td><td colspan="4">+ separate acellular vaccine<br>DT-IPV +aP</td><td colspan="7">acellular combined vaccine<br>DTaP-IPV</td></tr>
<tr><td>vaccine</td><td>RIVM-DTP</td><td colspan="4">Single aP added<br>RIVM/GSK</td><td colspan="2">Triaxis-polio</td><td colspan="5">Infanrix-IPV</td></tr>
</table>

**Figure 1** Vaccines, used for primary series and booster vaccination for birth cohorts 1991-2007. [a] = infants born between February 1st 2004 and November 1st 2004 received a mixed schedule of wP and aP. Abbreviations: wP, whole cell pertussis vaccine; aP, acellular pertussis vaccine; IOU, International Opacity Units.

Yet the force of infection remains high and is still increasing. Pertussis is endemic in the Netherlands with epidemic peaks every 2 to 3 years with numbers of reported cases ranging from 2847 (in 2003) to 9726 (in 2004). In 2011, 6891 cases were notified, in 2012 up to August 18, 10454 cases.

Strikingly the incidence in the first months of 2012 remained at the level of end of 2011, not decreasing as usual in late winter. As yet it is not clear whether the seasonal peak will come on top of this, once the season of pertussis begins, generally in September-November. See figures 2-4 and tables 1 and 2 for more detailed information on morbidity and mortality. In these tables and figures, years with a high peak in pertussis morbidity are compared.

**Table 1** Absolute number of notifications in 2012, based on reporting date.

| Month | Absolute number of notifications |
|---|---|
| January | 853 |
| February | 1052 |
| March | 1191 |
| April | 1270 |
| May | 1382 |
| June | 1945 |
| July | 1904 |
| August* | 857 |
| Total | 10,454 |

*= notifications until 18-8-2012 included
The relative low number of notifications in August may be a true decrease, but may also be due to decreased / delayed reporting during holidays.

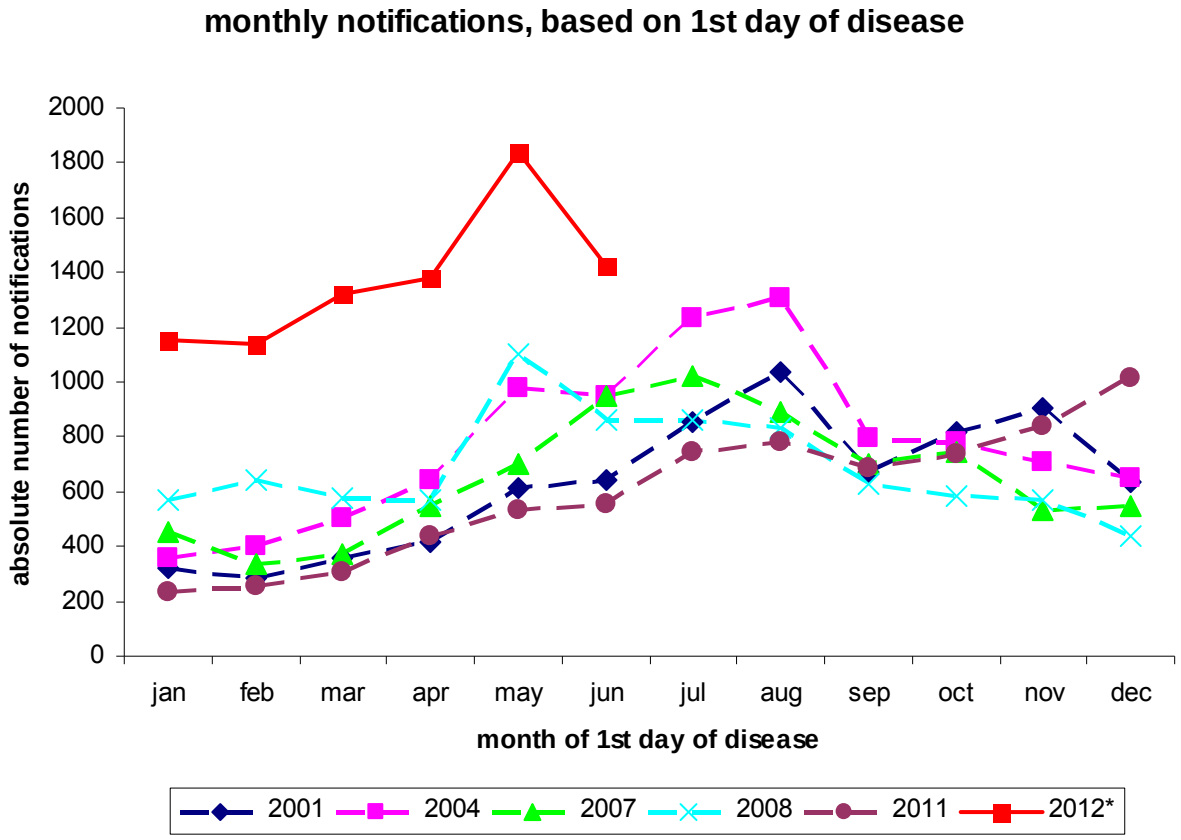


**Figure 2** Absolute number of notifications per month, based on day of onset; 2001, 2004, 2007, 2008, 2011 and 2012.
*= notifications until 18-8-2012 included. The decrease of notifications with day of onset in June 2012 may be a true decrease, but may also be due to decreased / delayed reporting during holidays.

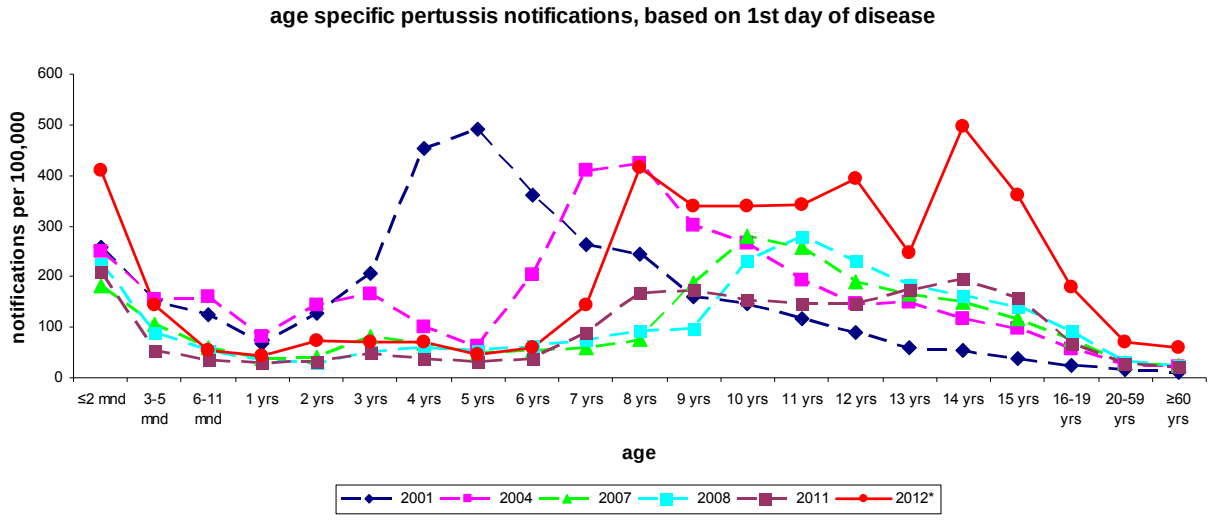


**Figure 3** Age-specific incidence rates of notifications, based on day of onset; 2001, 2004, 2007, 2008, 2011 and 2012.
*= notifications until 18-8-2012 included.

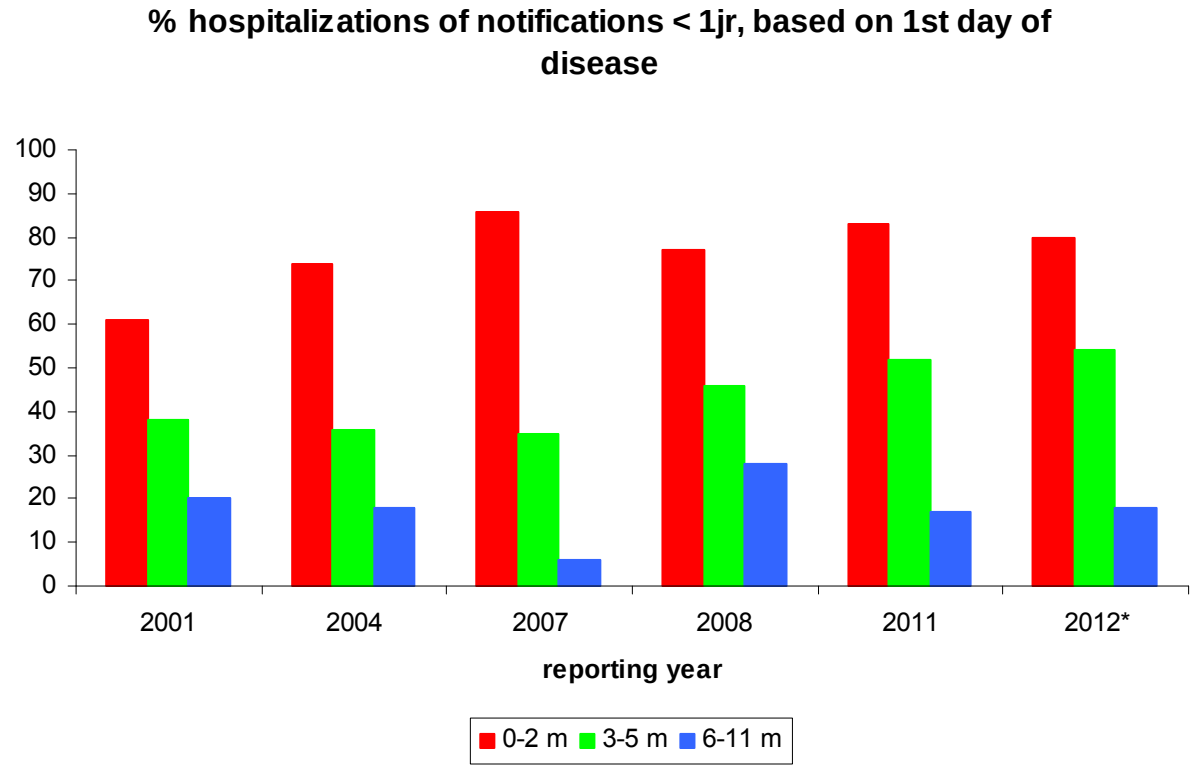


**Figure 4** Hospitalisations (percentage relative to number of notifications in infants); 2001, 2004, 2007, 2008, 2011 and 2012.
*= notifications until 18-8-2012 included.

Slight differences with table 2 because sometimes no information on hospitalisation is available.

**Table 2** Absolute number of hospitalisations and deaths; numbers vaccinated between brackets; 2001, 2004, 2007, 2008, 2011 and 2012.

| | 2001 | 2004 | 2007 | 2008 | 2011 | 2012* |
|---|---|---|---|---|---|---|
| Absolute number of notifications 0-2 m | 146 (36) | 131 (36) | 86 (16) | 103 (26) | 100 (36) | 89 (28) |
| Absolute number of notifications 3-5 m | 93 (38) | 76 (51) | 48 (28) | 42 (28) | 26 (18) | 31 (23) |
| Absolute number of hospitalisations 0-2 m among notifications | 65 (10) | 95 (23) | 73 (11) | 78 (14) | 71 (17) | 61 (14) |
| Absolute number of hospitalisations 3-5 m among notifications | 30 (12) | 25 (13) | 16 (9) | 17 (9) | 12 (8) | 15 (9) |
| Deaths 0 jr | 0 | 1 | 0 | 0 | 1 | 2 (0) |

*= notifications until 18-8-2012 included.

Since 1996, the number of reports of pertussis in adolescents and adults has increased considerably, also when taking into account a known substantial underreporting. It appeared from a seroprevalence survey conducted by RIVM in 1995-96, that 4.0% of the population above the age of 9 years had a recent infection with *B.pertussis*. This percentage more than doubled to 9.3% in 2006-07 (3). Most of these infections are mild with aspecific symptoms, which explains partly that only about 1% of infections is notified.

For cohorts that were eligible for a revaccination at the age of four with acellular vaccine (introduced in November 2001, for birth cohort 1998 onwards) the incidence of pertussis increased already some years after revaccination, despite the booster (figure 3). These cohorts received their primary series with a relatively weak whole cell vaccine, which might have contributed to the limited protection of the booster. However, a limited effect of the booster vaccination was also seen in the US population where acellular vaccines were used both in the primary series and as booster (4). Probably also the dose of the pertussis components present in the booster vaccine will influence the duration of protection. In the Netherlands from August 2006 to December 2007 a low dose vaccine, Triaxis, was used in the NIP, from January to September 2008 variably Triaxis and Infanrix (which contains a high dose of pertussis components) and from September 2008 Infanrix only. A low dose booster vaccine for whole cell vaccinated children induced low antibody levels after the booster (5). Up to now, too few data are available to decide on the role of the factors mentioned; children, born in 2005 (receiving both infant acellular vaccine as well as high dose acellular booster), will reach the age of 8 years (i.e. 3 years after the booster) in 2013.

Studies on cellular immunity after pertussis vaccination have shown that the change from cellular to acellular vaccine in 2005 has raised the T-cell responses after the primary vaccinations. There was a slight shift in the T-cell balance from T-helper-1 cells to T-helper-2 cells. Also IgG4 en IgE antibodies are induced by acellular vaccines (6). These shifts in immune responses may be associated with more allergic reactions (7) (8) (9).

The transition to acellular DTaP-IPV-Hib in 2005 resulted in an increase of the risk of (severe) local and systemic reactions after the booster dose at the age of four, so after the 5$^{th}$ acellular vaccination. The height of the T-cell responses, the disturbance of the balance between Th1- and Th2-cells after 4 high dose acellular vaccines and the increase in adverse events following immunisation (AEFI) after the preschool (5$^{th)}$ booster vaccine may be related. The RIVM and the Netherlands Pharmacovigilance Centre Lareb recently have started a case-control study into this relationship. It should be noted that,

despite the side effects of the booster vaccination, overall, acellular vaccines are less reactogenic than whole cell vaccines (10).

## 3 Neonatal vaccination

The first scenario aims to provide protection directly to the newborn at the earliest opportunity: a first dose of a pertussis containing vaccine soon after birth, either by advancing the first dose of DTaP-IPV-Hib-hepB or by adding a plain pertussis vaccine to the vaccination schedule.

### 3.1 Safety

Effect on the neonatal immune system.
It is often stated that the neonatal immune system is immature. However, it is now assumed that the immaturity reflects adaptation to the neonatal and early postnatal period. The neonatal immune response is biased against the Th1 cell polarizing cytokines in order to avoid immune reactions between the mother and foetus or excess inflammatory reactions. However, this bias against Th1 responses increases the susceptibility of the neonate to viral and bacterial infections (11). Further, the foetal adaptation may result in a Th2 polarisation after vaccination, as observed with acellular pertussis vaccines (12), conjugated pneumococcal vaccines (13), hepatitis B vaccine (14) and oral polio vaccine (15). Not all vaccines polarize towards Th2 in neonates and exceptions include BCG (16) and whole cell pertussis vaccines (17). This depends on the antigens, dose and the adjuvants present in the vaccines. Polarisation towards Th2 with respect to pertussis antigens is associated with a higher risk of adverse reactions after a booster at the age of four to six years (9) and induction of IgG4 and IgE antibodies. (6) It is not clear if early polarisation towards Th2 may result in a higher risk for atopy in the long term. According to Higgs et al., (17), pertussis vaccines which polarize towards Th1 are more effective than vaccines which polarize towards Th2. In the short term (i.e. days) significant adverse effects of neonatal vaccination have not been observed. (12, 18) Some vaccines (e.g. hepatitis B vaccine and BCG) have been used for neonatal vaccination for years, without evidence for long term adverse effects (19).

### 3.2 Immunogenicity and effectiveness

One remark in advance on immunogenicity: There is no clear correlate of protection defined for pertussis. Therefore, several studies use different methods to define seropositivity.

To be effective, neonatal vaccination needs to induce an earlier immune response than the traditional schedule and should not suppress immunity in the longer term. Indeed, studies in the 1960s revealed that neonatal vaccination with whole cell pertussis vaccines resulted in a lower immune response after subsequent doses (hyporesponsiveness) (20). Recently the effect of neonatal vaccination with an acellular vaccine was compared with control groups (Table 1). The control and experimental groups differed only in vaccination at birth, which was omitted for the control group. In some studies, however, HBV was used for neonatal vaccination in the control group. One study also included a booster at 1 month of age following neonatal vaccination and will be discussed separately (12). Three studies, which used a stand-alone pertussis vaccine for neonatal vaccination, gave very similar results (12, 18, 21). In all three studies, titers against pertussis antigens, determined between 2 and 7 months, were found to be equal or higher compared to the control group. One study also measured antibodies at 12 months and found lower titers against Ptx (21). A fourth study used a conventional vaccine for neonatal vaccination (DTaP) (22). Titers were determined at 7, 17 and 18 months. At 7 months lower titers were observed against all pertussis antigens, except FHA. At 17 months only titers against Fim were lower, while at 18 months lower antibody levels against all pertussis antigens were found. In the neonatal study that included a booster at 1 month, higher titers against pertussis antigens compared to the control group, were observed between 2 and 7 months (12). Bystander

effects leading to hyporesponsiveness were also investigated in most these studies. For this, titers were determined at 7 to 8 months. Hyporesponsiveness to Hib was found in two studies and against D and pneumococcal polysaccharide in one study. It should be noted that only antibodies against HBV, Hib, D, T were assessed in these four studies. Three studies assessed adverse effects and did not find differences with the control group. One study determined the effect of neonatal vaccination on Th1/Th2 polarisation and found a strong Th2 bias (23). Although the results of these small studies should be interpreted with care, they suggest that neonatal vaccination with a stand-alone vaccine induces an earlier immune response compared to the traditional vaccination schedule. After neonatal vaccination, less bystander effects were observed with a stand-alone vaccine compared to multicomponent vaccine. The effects of Th2 polarisation of the immune system need further study. Although the efficacy of neonatal vaccination has not been studied, it seems likely that this approach will reduce infant morbidity and mortality, as several studies have shown that one dose acellular vaccine at the age of 2-3 months results in a significant reduction in morbidity (24) (25-27). As titers of maternal antibodies will be higher in neonates compared to 2-3 months old infants, interference from maternal antibodies may be a more important factor to consider when applying neonatal vaccination. Maternal interference may be neutralised by increasing the dose of subsequent boosters. However, high-dose acellular boosters may induce more severe local side effects.

### 3.3 Cost-effectiveness

Estimates of the cost-effectiveness of the neonatal vaccination are scarce. One analysis, based on Dutch incidence and cost data, concludes that it would not be cost-effective, with a cost-effectiveness ratio of more than €300,000/QALY gained (2008 prices) (28). Preliminary calculations performed by CIb confirm that this strategy would not be cost-effective for the Dutch situation (>€400,000/QALY gained). A study from Australia also showed very high cost-effectiveness ratios for the option of neonatal vaccination (29).
According to calculations of CIb, vaccinating one cohort of newborns would cost about €5 million (2009 prices).

### 3.4 Feasibility and operational aspects

An advantage of neonatal vaccination is the accessibility of the neonate. The logistics of vaccinations is particularly simple when the birth occurs in a hospital setting, but becomes more complex in the case of birth at home. Midwifes could play a role in neonatal vaccination. Indeed, midwifes vaccinate hepatitis B positive mothers to prevent perinatal transmission. However, this involves relatively few cases and vaccination of all newborns requires a more extensive organisation and would involve significant costs. Possibly the vaccination can be given by the team which collects blood from newly born by heel prick within 7 days after birth. The vaccination should be part of the NIP to cover the costs and warrant equal access.

### 3.5 Known unknowns

- Efficacy of one neonatal dose. Which vaccine to be used: Pertussis stand-alone or DaKT-IPV-Hib-HBV combination vaccine.
- Implications of a neonatal dose for timing and number of following doses.
- Availability of a stand-alone pertussis vaccine.
- (long) term effect of (a temporary?) Th2 polarisation of the neonatal immune system.
- Possible interference with maternal antibodies.
- Effect neonatal vaccination of preterm neonates.
- Acceptability of neonatal vaccination by the parents and whether the target group can sufficiently be reached.

### 3.6 Summary

Two studies have found that neonatal pertussis vaccination initially accelerates the antibody response to pertussis antigens. Later, after 7-8 months, the picture was divers and both increases and decreases in antibody responses to pertussis antigens were observed relative to a control group. A suppression of immune responses against co-administered, non-pertussis antigens, was also observed. There is some concern that neonatal vaccination with current pertussis vaccines may polarise the infant immune system towards a more Th2 response and that Th2 responses may be associated with side-effects of booster vaccinations and atopy in later life. It should be noted, however, that some vaccines (e.g. BCG, IPV and HBV) have been administered to neonates for years without evidence for (long-term) adverse effects. There are no data on the efficacy of neonatal pertussis vaccination. However, one dose of an acellular pertussis vaccine given to infants 2-3 months old was shown to result in a significant decrease in morbidity. Thus, it seems likely that neonatal vaccination can reduce the period in which the infant is not protected against pertussis from 8-10 weeks to 2-3 weeks. An advantage of neonatal vaccination is that the infant is generally easily accessible in health care settings. Further, the current vaccination schedule for infants does not have to be adapted. Preliminary calculations performed by CIb suggests that neonatal vaccination would not be cost-effective under the Dutch circumstances. In view of the uncertainties of neonatal vaccination, it can be considered to use a monocomponent vaccine containing pertussis toxin only. This may prevent hyporesponses to antigens used in subsequent vaccinations. Further, pertussis toxin is not only important for infection and transmission, but probably the major cause of neonatal mortality due to pertussis (30). Together with maternal vaccination or cocooning vaccination of parents, neonatal vaccination is the only possibility to reduce infant pertussis in the short term.

**Tabel 3** Neonatal studies with acellulair pertussis vaccines.[1]

| Study | Belloni | Halasa | Knuf | Wood | Wood |
|---|---|---|---|---|---|
| Vaccine at birth | aP | DTaP | aP | aP | aP and 1 m |
| Producer | Chiron | Sanofi | GSK | GSK | GSK |
| Composition | Ptx,Prn,FHA | Ptx,Prn,FHA,Fim | Ptx,Prn,FHA | Ptx, Prn, FHA | |
| Schedule | 0,3,5,11 m | 0,2,4,6,17 m | 0,2,4,6 m | 0,2,4,6 m | 0,1,2,4,6 m |
| Bp antib 2-3 $m^2$ | **Ptx,Prn,FHA** | Nt | **Ptx,Prn,FHA** | **Ptx,Prn,FHA** | **Ptx,Prn,FHA** |
| Bp antib 4-5 $m^2$ | **Ptx,Prn,FHA** | Nt | **Ptx,Prn,FHA** | **Ptx,Prn,FHA** | **Ptx,Prn,FHA** |
| Bp antib 6-7 $m^2$ | **Ptx,Prn,FHA** | **Ptx, Prn, FHA, Fim** | **Ptx,Prn,FHA** | **Ptx,Prn,FHA** | **Ptx,Prn,FHA** |
| Bp antib 12 $m^2$ | **Ptx,Prn,FHA** | Nt | | | |
| Bp antib 17 $m^2$ | | **Ptx, Prn, FHA, Fim** | | | |
| Bp antib 18 $m^2$ | | **Ptx, Prn, FHA, Fim** | | | |
| Bystander effect | | **HBV,Hib,D,T, IPV1,2,3, PVC (7 m)** | **HBV,Hib,D,T, IPV1,2,3 (7 m)** | **HBV,Hib,D,T (8m)** | **HBV,Hib,D,T (8m)** |
| Th1/Th2 polarisation | Nt | Nt | Nt | Th2 polarisation | |
| Adverse effects [5] | Nt | No difference | No difference | No difference | |

[1]Antibodies responses in neonatally vaccinated infants were compared to infants vaccinated according to the normal schedule (control group).
[2] Antibody responses to pertussis antigens measured in the indicated period compared to the control group. Black, blue and red indicate no (significant) difference, significant higher and significant lower titers, respectively, compared to the control group.
[3] Bystander effect on non-pertussis antigens co-administered during the normal schedule. Black, blue and red indicate no (significant) difference, significant higher and significant lower titers, respectively, compared to the control group. The month during which the blood sample was taken is indicted between brackets.
[5] Adverse effects compared to the control group.
Studies: (12, 18, 21-23, 31)
Abbreviations: M, months. Nt, not tested.

# 4 Maternal immunisation

The second scenario aims to provide the newborn with protection by vaccinating the mother at the end of pregnancy. This will result in passive transplacental transfer of antibodies from the mother to the unborn child and also in indirect protection after birth as the immune mother will not be a source of transmission of pertussis to her child.

## 4.1 Safety

Safety of maternal immunisation must be divided into reactogenicity in general and pregnancy related safety issues. The overall reactogenicity for maternal immunisation is identical to that of adult vaccination in general.

### 4.1.1 Overall safety

Blatter et al. compared de reactogenicity of 3- vs. 5-component DTaP-vaccine in 19-64 year old adults. Local reactions and a temperature of ≥ 37.5°C were reported frequently (≥61% and ≥5.5%, respectively), significantly more often in the group receiving the 5-component vaccine compared to the group vaccinated with the 3-component vaccine (32). Regularly (re)vaccination with DT-IPV or TT is given for travelling or injury. A French study showed that administration of DT-IPV 1 month before vaccination with DTaP-IPV did not alter the safety profile of the latter vaccine compared to a control group without a preceding vaccination (33). This was confirmed by Talbot et al. who studied Td or TT vaccination followed by TdaP vaccination with an interval < 2 years compared to an interval ≥ 2 years. He found that the percentages of moderate and/or severe adverse events following TdaP did not significantly differ between the group with the short interval and the group with the long interval (34). Halperin et al. concluded TdaP could be safely administered at an interval of 18 months or more after a previous TD/Td vaccine, although there was a slight increase in injection site events with decreasing interval since a previous immunisation (35).
According to American Academy of Pediatrics (AAP), intervals of less than 5 years for administering TdaP can be used. Data since 2005 support an acceptable safety with an interval as short as 2 years between Td and DTaP vaccination(36).
According to ACIP breastfeeding following vaccination of the mother is allowed (http://www.cdc.gov/vaccines/pubs/preg-guide.htm#bfeeding).

### 4.1.2 Pregnancy-specific safety

Maternal immunisation against tetanus has been used worldwide since the 1970s and no evidence has been presented for negative effects on pregnancy or the neonate (37),(38). More recently, 10 vaccines recommended for maternal immunisation have been tested for safety for mother and child (see(39) for a review). As yet no evidence has been found that any of these vaccines cause unacceptable side effects. In particular, maternal immunisation with influenza has been the subject of a number of studies (40-43). In the most recent study, based on 6,600 infants, it was found that exposure to an adjuvanted inactivated influenza vaccine during pregnancy was not associated with a significantly increased risk of major birth defects, preterm birth, or fetal growth restriction (42, 43). Inactivated influenza vaccine is currently recommended by the US Centers for Disease Control and Prevention for all pregnant women with high risk factors for severe influenza and for those women who will be in the second or third trimester during the influenza season (44-46).

Studies addressing the safety of maternal pertussis vaccination have generally been based on passive surveillance systems and on a limited number of participants. In one study 132 reports of adverse effects, following maternal immunisation, to the Vaccine Adverse Event Reporting System (VAERS) were analysed. The results were compared to maternal influenza immunisation which was assumed to be safe. According to the authors, concerning patterns in maternal, infant or fetal outcomes were not identified (47). In two other studies, based on 52 and 16 pregnant women, no adverse events were found after maternal immunisation with acellular pertussis vaccines (34) (48) (34, 48).
At present, two clinical trials of acellular pertussis vaccines administered during the third trimester of pregnancy are underway in Canada (49) and the USA (50). Both are evaluating the safety and

immunogenicity of acellular vaccines in pregnant women and measuring the response to routine pertussis active immunisation in their infants (www.clintrial.gov).
There is some evidence that high levels of pre-existing immunity in adults are a risk factor for local side-effects of vaccination (51). Therefore, it may be necessary to screen pregnant females before vaccination. It should be noted however, that a short interval between Td/TT and a single dose of TdaP is safe (35), (34).The USA Advisory Committee on Immunization Practices (ACIP) has concluded that "available data from these studies did not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received TdaP". The studies referred are based on data from VAERS, Sanofi Pasteur (Adacel) and GlaxoSmithKline (Boostrix) pregnancy registries and two small studies (34), (48). The ACIP concluded further: "From a safety perspective, ACIP concluded that administration of acellular vaccine (TdaP) after 20 weeks' gestation is preferred to minimize the risk for any low-frequency adverse event and the possibility that any spurious association might appear causative" (52).

## 4.2 Immunogenicity and effectiveness

Many studies have shown that antibodies confer protection against pertussis (reviewed in (53)) and a lack of maternal antibodies has been proposed to be a risk factor for infant pertussis (54). Further, maternal antibodies against pertussis antigens are transferred efficiently to the unborn child(48, 55-58). Studies in the 1940s and 1950s with whole cell vaccines have provided some evidence that maternal immunisation may be effective (reviewed in(53)). In one study the incidence of pertussis in a group of 100 babies of immunised mothers was compared with an equal number of babies of un-immunised mothers(59). In the first 6 months of infancy, there were six exposures in the un-immunised group, resulting in three cases of pertussis. During the same period there were eight exposures in the immunised group, but no cases of pertussis developed. In the second 6 months of life each group yielded two cases of pertussis. The latter finding suggests that the passive immunity conferred to the babies did not persist after 5–6 months of age. Based on this small study one can speculate that interference of infant vaccination by maternal antibodies will not occur in infants 5-6 months old. Experience with other toxin-mediated diseases such as diphtheria and tetanus and with viral disease (e.g. influenza) have provided evidence that maternal immunisation can be effective (60-63). Peters et al studied the potential impact of maternal immunisation (≥2 weeks prior to delivery) and estimated from US data that 625 to 3204 of pregnant women should be vaccinated in order to prevent one newborn from being hospitalised with pertussis (27). Numbers decrease and thus the impact increases when also the father is vaccinated (at the same time) and when the possible impact on future children is included.
At present, as result of the start of pertussis vaccination within the National Immunisation Programme in 1957 and the continued high vaccination coverage, most parents will have been vaccinated with whole cell DTP-IPV vaccine during infancy. From ~ 2025 onwards, mothers, vaccinated with 5 doses of aP, will give birth. Presumably, the immune response of mothers primed with acellular vaccines will be superior to those who received their primary series with a whole cell vaccine.

Maternale interference or blunting.
A concern associated with maternal immunisation is interference with childhood vaccination, because preexisting antibodies gained by placental transfer might affect the infant's immune response to primary immunisation. It is assumed that the primary cause for maternal interference is epitope masking by maternal antibodies, preventing antigen binding by infant B cells (64). The inhibitory effect is dependent on the ratio between maternal antibodies at the time of vaccination and the amount of antigen used to vaccinate the infant. Interference by maternal antibodies has been observed with whole cell, but not, or to a much lesser extent, with acellular vaccines, presumably because of the higher antigen content of the latter (58, 65, 66).

## 4.3 Cost-effectiveness

A study for the Netherlands concludes that the maternal strategy could be cost-effective (€3,500/QALY gained) (2008 prices) (28). The reason that this strategy would be more cost-effective than the neonatal strategy is due to the QALY gain because of the averted infections in the mothers. This result is based on an assumed underreporting of 200 times the notifications of adults, and assuming a QALY loss also in the underreported cases. With less underreporting and lower QALY loss in the underreported cases, the cost-effectiveness becomes less attractive. Preliminary calculations made by CIb show unfavourable cost-effectiveness ratios (>€200,000/QALY gained) (2009 prices). Differences in results of the Dutch studies

are caused by different assumptions, mainly regarding the factor underreporting (100 vs. 200 times) and the QALY losses due to length of symptomatic illness (6 weeks vs. 3 months).
According to calculations of CIb, vaccinating one cohort of first time mothers would cost about €2.5 million per year (a catch-up vaccination campaign would cost about €5 million per year).

### 4.4 Feasibility and operational aspects

An advantage of maternal immunisation is the accessibility of the target group, since (pregnant) mothers frequently visit health-care centres. It was shown that the acceptance of influenza vaccination by pregnant mothers during the influenza pandemic in 2009 amounted to about 60% (67). It has to be seen whether the same goes for pertussis vaccination. It would be advisable to investigate the acceptance of pertussis vaccination by pregnant women in a pilot study or a Discrete Choice Experiment.
Further, apart from cost-effectiveness, is should be considered how the costs of vaccination outside the NIP should be covered. Could pertussis vaccination during pregnancy be included in the basic health insurance?

### 4.5 Known unknowns

- The level of maternal antibodies required for protection of the child in the period which is not covered by active immunisation.
- The level of antibodies which will not interfere with primary immunisation of the newborn from month 2 onwards
- Protection of premature infants who may be deficient in protective antibodies, since transfer of maternal antibodies reaches its maximum during the last few weeks of pregnancy.
- Acceptability by target group and whether the target group can sufficiently be reached.

### 4.6 Summary

Maternal immunisation may substantially reduce pertussis morbidity and mortality in infants too young to be fully vaccinated (for reviews see (39, 53, 68)). A major obstacle for its introduction is concern about side-effects in mother and child. However, maternal immunisation has been shown to be effective and safe for a number of vaccines over long periods of time. Passively collected data on vaccination of pregnant women with acellular pertussis vaccines have not revealed adverse effects on the pregnancy or for the child. Because maternal immunisation transfers immunity to the infant through antibodies, it is significant that studies in animals and human beings have shown that antibodies confer protection against pertussis. An important gap in our knowledge is the level of maternal antibodies required for protection of the child in the period which is not covered by active immunisation. However, acellular vaccines induce high levels of antibodies against known "protective" antigens. Maternal immunisation is highly efficient as it protects two persons with a single vaccination. Based on current evidence the USA Advisory Committee on Immunization Practices (ACIP) recommends vaccination of all pregnant women with acellular pertussis vaccines.

## 5 Cocooning

The third scenario aims to raise (herd) immunity among acquaintances of newborns, thus providing indirect protection. Primarily parents of newborns could be targeted (scenario 3a), but the concept of cocooning could be widened to others, such as professionals in close contact with newborns (scenario 3b).

### 5.1 Vaccination of parents of newborns – cocooning

Several countries have implemented cocooning in order to further reduce pertussis burden and protect the most vulnerable group, i.e. very young infants. Individual parents can decide to be vaccinated in order to protect their newborn, but the success of cocooning for public health largely depends on high vaccination coverage. Due to the maternity leave, mothers are easily targeted, but fathers may be hard to reach. Several studies show that mothers are important in transmitting pertussis to newborns. (69) (70).

### 5.1.1 Safety

Reactogenicity of vaccination of parents of newborns is similar to that found for all adults. See the paragraph on safety of maternal vaccination for detailed information. At present, as result of the start of pertussis vaccination within the National Immunisation Programme in 1957 and the continued high vaccination coverage, most parents will have been vaccinated with whole cell DTP-IPV during infancy. From ~ 2025 onwards, mothers, vaccinated with 5 doses of acellular vaccine, will give birth.

### 5.1.2 Immunogenicity and effectiveness

Both pre- and post-licensure studies of acellular pertussis containing vaccines, licenced for adults, showed sufficient antibody-responses after vaccination (36). A trial, conducted with a 5 component acellular TdaP, showed higher antibody levels in adolescents and adults compared to infants (71, 72). However, the antibody-level decreased with 50% within 1 year after vaccination (73). Ward et al. demonstrated a vaccine efficacy of 92% (95%CI 32%-99%) against pertussis (defined as coughing lasting for 5 days or more that was clinically, microbiologically and serologically evaluated) in 2781 persons between 15 and 65 years of age during a follow up of 2.5 years following vaccination, with either a 3-component single aP vaccine (GSK) or hepatitisA vaccine (GSK) (74).

In relation to the cocooning strategy, information on the prevention of pertussis transmission to newborns is more relevant. The efficacy for the prevention of transmission is lower than the efficacy for prevention of symptomatic pertussis. In a Dutch household transmission study including 164 hospitalised infants, for 96 households (60%), the most likely source of infection of the infant was established, being a sibling (41%), mother (38%), or father (17%). According to a recent paper, based on this large-scale transmission study in the Netherlands, ~50% of infant pertussis cases could be prevented by immunisation of the mother, whereas vaccination of fathers is less effective. (69), (70). According to this study (69), vaccinating both mothers and fathers was expected to reduce pertussis in infants with at least 55%. It was shown that vaccinating siblings in addition to parents as part of cocooning strategy further reduced infant pertussis, ca. 90% in total. Since a preschool booster is included in the Dutch NIP, this benefit is probably already achieved to a considerable degree. Castagnini et al. conducted a cross sectional study to evaluate the impact of maternal postpartum TdaP vaccination on infant pertussis infection and found no difference in pertussis illness in infants < 6 months of age (75). Several countries, i.e. United States, Belgium, France and Germany, already recommend vaccination of household members or other groups in close contact to young infants in order to prevent pertussis in newborns (76).

### 5.1.3 Cost-effectiveness

A study from the Netherlands indicates that cocooning can be cost-effective mainly due to the beneficial effects to the parents, assuming a 200 times underreporting with a QALY gain in these cases when averted (28). However, preliminary results of a cost-effectiveness analysis performed by CIb, shows that the cocooning strategy could reduce the disease burden in infants and mothers vaccinated, but the costs involved are high according to acceptable cost-effectiveness thresholds (> €400,000/QALY gained) (2009 prices). Including fathers in the vaccination would cost even more per QALY gained. Differences in results of the Dutch studies are caused by different assumptions, mainly regarding the factor underreporting (100 vs. 200 times, i.e. one out of 100 vs. 200 cases notified) and the QALY losses due to length of symptomatic illness (6 weeks vs. 3 months).
Vaccinating one cohort of first-time mothers would cost around €2.5 million, a catch-up campaign including all new mothers about €5 million.
A study performed for the Australian situation also showed an unacceptable high cost-effectiveness ratio for the cocooning vaccination strategy (parental vaccination) (29). Calculations of number of parents that need to be vaccinated (NVV) in order to protect an infant from hospitalisation or even death obviously depend on the incidence rate of infants obtaining pertussis. In provinces in Quebec and British Columbia, the risk of infant pertussis-related death over 2005-2009 was <0.5 per 100,□000. The NNV for parental immunisation was at least 1 million to prevent one infant death and >10,000 for hospitalisation. Therefore, at low pertussis incidence, the parental cocooning programme is inefficient and resource intensive for the prevention of serious outcomes in early infancy (77). Based on US data, the potential impact of immunisation of the mother in hospital shortly after giving birth or 2 weeks later at the healthy

baby clinic consultation was estimated: 703 to 3950 resp. 804 to 5147 women to be vaccinated in order to prevent one newborn from being hospitalised with pertussis (27).

#### 5.1.4 Feasibility and operational aspects

Vaccination of mothers soon after birth could be done by either midwife/obstetrician or general practitioner. Also it could be considered to assign this task to the screen teams who visit the family in the first week after birth for neonatal screening (bleeding by heel puncture).
Immunising fathers as part of the cocooning policy seems logistically less feasible as fathers are mostly not at home after the birth of a child while the mothers are on pregnancy leave, so it will be much more difficult to reach fathers.
Further, apart from cost-effectiveness, is should be considered how the costs of vaccination outside the NIP should be covered. Could pertussis vaccination of parents be covered by basic health insurance or should the parents be charged?

#### 5.1.5 Known unknowns

- Duration of protection of the mother in the view of transfer of antibodies to possible future infants and the necessity to revaccinate after a next pregnancy.
- Interval to last immunisation, number of doses needed
- Acceptability by target group and whether the target group can sufficiently be reached.

#### 5.1.6 Summary

Vaccinating young mothers and fathers has been extensively studied and is regarded as safe. All acellular pertussis containing vaccines, licenced for adults, show sufficient antibody-responses after vaccination. Preliminary results of a cost-effectiveness analysis performed by CIb, shows that the cocooning strategy is not cost-effective, according to currently used cost-effectiveness thresholds.
Until now, only moderate vaccination coverage of post-partum women was reached in countries that implemented cocooning. Fathers and other family members were hard to include (78, 79). According to Castiagnini et al. it is important to reach as much household members as possible to create a complete cocoon and not just vaccinate mothers. His cross sectional study suggests no impact of vaccination of post partum mothers on infant pertussis infections (75). However, modelling of transmission rates in the household based on a large household transmission study, performed by CIb, shows that ~ 50% of infant pertussis infections can be prevented by vaccinating the mother. (69), (70).

### 5.2 Vaccination of professionals in close contact with newborns – cocooning

The cocooning approach of vaccinating close contacts in order to protect the newborn indirectly could be reasonably extended to health care workers (HCW) in neonatal intensive care units and in paediatric wards. Also midwives could be targeted. For personnel in day-care centres where young babies are staying vaccination could be considered as well.

#### 5.2.1 and 5.2.2 Safety, immunogenicity and effectiveness

No specific remarks need to be made with respect to safety and immunogenicity, as these issues are comparable with vaccination of parents (see 5.1). The effectiveness in protecting newborns can be expected to be lower compared to vaccination of household members as the contacts of professionals with the babies may be less frequent and intensive.

#### 5.2.3 Cost-effectiveness

A Canadian study shows cost-effectiveness upon immunising health care workers in paediatric health care centres (80). No data on cost-effectiveness for the Netherlands are available. We may assume that the cost-effectiveness is not favourable as in our country infants do not go to day care centres before three months of age; at that time they have been vaccinated at least once.

### 5.2.4 Feasibility and operational aspects

Even when the cost-effectiveness is questionable, it may be regarded as a matter of due care to vaccinate professional groups around the newborn. However, it is subject to ethical debate whether you can require professionals to be vaccinated for the benefit of those who are put under their care, while the vaccinees will not or hardly benefit from the vaccination themselves.

Vaccination could be delivered as part of care provided by the Health and Safety Executive depending on available resources. It would then be helpful to include the need for pertussis immunisation of professionals in child care (both medical and social) in protocols for health and safety care.

### 5.2.5 Known unknowns

A study into the acceptance by professionals is going on (University of Nijmegen). The results of the study are expected in spring 2013.

### 5.2.6 Summary

The cost-effectiveness of vaccination of professionals with close contact with infants in order to protect these infants, is so far unknown, but probably low. Employers of these professionals should verify their vaccination status and, in case susceptibility can be assumed, it should be considered to offer vaccination.

## 6 Pertussis vaccination before pregnancy (pre-conception immunisation)

The fourth scenario -in line with the rationale of vaccinating the mother during pregnancy- is to vaccinate mothers to be, i.e. before pregnancy (81).

### 6.1 Safety

As it is known that pertussis vaccination during pregnancy does not involve a safety issue, this is probably also true in the event that conception occurs shortly after a pertussis vaccine is administered.

### 6.2 Immunogenicity and effectiveness

See paragraph 5.1.2 on cocooning for data on immunogenicity.
Even when immunogenicity is good in adults, the effectiveness of this scenario may be questioned; with good results on the individual level, impact on the population level requires a programmatic approach of preconception care.

### 6.3 Cost-effectiveness

The cost-effectiveness has not been assessed and needs a broader view than the calculations for a cocooning strategy only targeting mothers, to be able to include effects on the transmission to other household members and contacts.

### 6.4 Feasibility and operational aspects

A committee of the Dutch Health Council who advised the minister of health on preconception care recommends to offer programmatic preconception care to the Dutch population (82). The evaluation of the mother's vaccination status, particularly for rubella, measles and pertussis, could then be part of the preconception consultation; this implies consideration to (re)vaccinate when appropriate. So far, no programmatic preconception care has been established.
Further, apart from cost-effectiveness, it should be considered how the costs of this vaccination should be covered. Once a preconception consultation is financed and has become current practice, the coverage of vaccine and vaccination costs has to be addressed. Possibly this could then be included in the basic health insurance.

### 6.5 Known unknowns

- Persistence of protection after the booster
- Independent cost-effectiveness analysis
- Acceptability by target group and whether the target group can sufficiently be reached.

### 6.6 Summary

Although less effective than maternal immunisation in the third trimester of pregnancy, it is worthwhile considering vaccination of women with a known wish to become pregnant.
The effect of a pre-pregnancy booster may have already decreased at the moment that the woman gives birth, so there may be doubts whether the antibody levels will be sufficient to provide passive protection to her baby during the period in which protection is not induced by active immunisation. It might then give a false sense of security. There are less doubts on the duration of (memory) immunity of the mother and so on the indirect protection to her newborn - if it is assumed that she will become pregnant again at least within a few years.
Pertussis vaccination before pregnancy is a safe– even when conception occurs shortly after vaccination of the mother-to-be, as well as an effective approach, at least at individual level. However, the impact on the population level may be questioned. The cost-effectiveness has not been assessed.

Preconception immunisation though potentially effective and even desirable on an individual level, will not be feasible as long as a preconception consultation will not be current practice and no rules for reimbursement are available.

## 7 Re-vaccination of older children and / or adolescents in order to reduce pertussis in newborns

The fifth scenario aims to raise immunity in the population and to reduce the force of infection in general by revaccinating older children and / or adolescents.

### 7.1 Safety

See also information on safety of maternal immunisation, paragraph 4.1.
Reactogenicity of adolescent and adult pertussis boosters has been extensively studied, both in pre- as well as in post-licensure studies (36, 83, 84). The safety of 5 acellular pertussis vaccines was compared in a multicenter, randomized, double-blind trial. Minor injection site reactions were common and similar in frequency among vaccinated groups. Late-onset injection site reactions were seen in all ACV groups. In children it is known that repeated doses of acellular pertussis vaccine increase the risk of (severe) local reactions and systemic adverse events (51, 85-87). Using adult formulations could reduce this risk (71), although local reactions occur frequently. A study exploring the reactogenicity of repeated pertussis booster, containing adult formulations, revealed local reactions in 70% of the participants following the second dose. For all three aspects (pain, redness and swelling) the percentage reported after the first dose was lower compared to the percentage reported after the booster. For pain and redness, the difference was 4.3%, for swelling this was significantly more (88).

### 7.2 Immunogenicity and effectiveness

See information on immunogenicity and effectiveness of cocooning, paragraph 5.1.2.
However, in the context of preventing pertussis in newborns, the efficacy against pertussis transmission is the most relevant outcome parameter. As already mentioned, transmission of pertussis to infants is mainly due to infection of the mother, father or the siblings (70). So far, there is no evidence that offering adolescents and adults a single booster vaccination, as performed in Germany, France, US, Canada and Australia have an impact on severe pertussis in infants (WHO 2010). Indeed, it is doubtful whether there is benefit for infants in boostering adolescents as they are unlikely to be in direct contact with infants. A recent study in Norway showed that the timing of incidence peaks is age group dependent, with a summer peak for infants, a summer-winter peak for parents and a winter peak for

adolescents (89). In addition, vaccination of adolescents and waning immunity may shift the disease burden to young adults. This is potentially harmful as especially young adults are likely to become parents and therefore in close contact with infants.

### 7.3 Cost-effectiveness

A recent Dutch cost-effectiveness analysis, using a dynamic model, of pertussis booster vaccination of one cohort, concludes that a pertussis booster strategy at the age of 12 is cost-effective in preventing pertussis in this specific cohort (90). Also, the estimates show a shift in pertussis in the vaccinated cohort of 12-year-olds to a higher age. It should be stressed that this then could pose an additional risk when these people are becoming parents. Anyway, that study did not explicitly apply a transmission model and thus did not assess the impact on newborns, which is the focus of this paper. The cost for the vaccination programme would be around 107.4 million for one cohort of 12 year olds (2011 prices).
The implementation of the booster dose at 4 years of age in the Dutch NIP was above the unofficial cost-effectiveness threshold (91). De Greeff et al. stated that the economic burden of pertussis in the Netherlands is largely determined by costs per infant case and only to a limited degree by costs per patient in other age groups. Therefore, to be able to assess the impact of an adolescent booster on newborns, a dynamic transmission model needs to be developed where the effect on transmission on different generations (cohorts) is included. One Dutch study on the cost-effectiveness of a booster vaccination in 12-year-olds indeed included indirect effects by using a dynamic model and shows an effect of reduced primary infection in infants, but also an increase in ages >20 (92). The booster at 12 years of age was considered cost-effective, but the analysis was sensitive to the assumptions made about length of immunity and the disease burden in adults; also it should be noted that the study assumed a high underreporting of 660 times (one out of 660 cases notified) (92). Again, these results stress that more reliable data on disease burden in adults, which is largely lacking, is needed, as this has a substantial influence on the cost-effectiveness ratio.

### 7.4 Feasibility and operational aspects

Different age groups could be considered for this revaccination policy. Either age groups that are eligible for vaccination within the NIP, or adults beyond the scope of the NIP. Now the scope of the NIP is up to the age of 19 years and the last youth health care consultation is scheduled at the age of 12 years. Revaccination within the NIP gives access to the expertise of the GGD (Public health Services, PHS) and allows for easy contact with and thus optimal coverage of the target group; invitations can be produced from the vaccination register Praeventis which is based on the population register. This could be an option when it would be decided to include revaccination of adolescents in the NIP.

### 7.5 Known unknowns

- As the relative contribution of adolescents as sources of infection in newborns may be limited (as a result of contact patters) the tentative impact is expected to be limited.
- Acceptability by target group
- What coverage will be reached and can herd immunity reasonably be expected?
- Correlate of protection, how long will the induced protection persist after one dose?
- Should we use the infant (high dose) or adult (low) dose vaccines? The high dose vaccine may give more side effects but induce longer lasting immunity.
- Data on disease burden in adults.

### 7.6 Summary

Immunogenicity of adolescent and adult pertussis vaccination is good and exceeds immunogenicity in infants. However, antibody-levels decline rapidly.
Also, reactogenicity is well documented, with local reactions frequently occurring. Extensive Limb Swelling, known in infants after a fifth booster dose, is very uncommon when adult formulations are used.
Most studies state that adolescent and/or adult boosters are cost-effective, although results are very sensitive to incidence rates, vaccine costs and country specific thresholds. Information on cost-effectiveness of large scale adolescent booster aP programmes in relation to reduce morbidity in infants, is lacking, but contact patterns show little impact on infant morbidity is to be expected.

Transmission of pertussis to infants is mainly due to infection of the mother, father or the siblings (70). So far, there is no evidence that offering adolescents and adults a single booster vaccination, as performed in Germany, France, US, Canada and Australia, has an impact on severe pertussis in infants (WHO 2010). Indeed, it is doubtful whether there is benefit for infants in boostering adolescents as they are unlikely to be in direct contact with infants. A recent study in Norway showed that the timing of incidence peaks is age group dependent, with a summer peak for infants, a summer-winter peak for parents and a winter peak for adolescents (89). In addition, vaccination of adolescents and waning immunity may shift the disease burden to young adults. This is potentially harmful as especially young adults are likely to become parents and therefore in close contact with infants

# 8 Vaccination schedules

Most pertussis primary vaccination schedules have a long history and have not been changed after the replacement of whole cell vaccines by acellular vaccines. Changes in the schedules are rare and consisted mostly of addition of booster vaccinations at later ages. Changes in the primary series by shifting the first vaccination to an earlier age (from 3-4-5 to 2-3-4 months in the Netherlands) were implemented to narrow the window of susceptibility.
All schedules with a booster in the first or second year of life, independent of the timing of the primary series, seem to provide protection against pertussis disease on a short-term basis; the preschool booster has shown its effectiveness during childhood. However, there is evidence that protection conferred by whole cell and acellular pertussis vaccines and/or vaccination schedules is insufficient in the long run. This section will focus on the primary series and preschool boosters, as this part of the vaccination programme has the highest impact on infant pertussis.

## 8.1 Safety

Almost all industrialised countries use the acellular vaccines in their primary series and boosters (EUVAC.NET: http://www.euvac.net/graphics/euvac/vaccination/vaccination.html). Use of acellular vaccines reduced the number of adverse events significantly compared with the use of whole cell vaccines (10). Recently, an increase in the local and systemic reactions after the acellular booster vaccination at 4 years of age was observed, when acellular vaccine was used in the primary series instead of whole cell vaccine, suggesting the side effects may be caused by the high dose of pertussis antigens (7).

## 8.2 Immunogenicity and effectiveness

Although the pertussis vaccination schedules used differ greatly between the industrialised countries, they now all follow more or less a similar scheme: a primary series of vaccinations in the first half year of life followed by a booster at the end of the first year or in the second year of life. In addition, a preschool booster is very often implemented and in some countries an adolescent booster and/or adult boosters are recommended.

### 8.2.1 Primary series and first booster

Of the 32 European countries listed on the ECDC website, the majority use a 2-4-6 schedule (12 countries) or a 2-3-4 schedule (9 countries) for the primary series. The reduced 2-4 schedule is used only in 2 countries (Italy, Slovak republic) and the reduced 3-5 schedule in the 5 Scandinavian countries. A minority of 4 countries uses 3 primary vaccinations starting at the 3rd month (3-4-6 or 3-4-5). In all 32 countries, except UK and Ireland, the primary series is followed by a booster vaccination implemented between 10 and 24 months. In most countries (25) the booster is administered between 12 and 18 months (http://ecdc.europa.eu/en/activities/surveillance/euvac/schedules/Pages/schedules.aspx ).
Although long term immunogenicity and efficacy data are scarce or non-existing, the following variations in the vaccination schedule that are expected to have a large impact on infant pertussis will be discussed: 1. timing of the first vaccination, 2. spacing between the primary vaccination series and 3. timing of the first booster.

#### 8.2.1.1 Timing of the first vaccination

In light of the recent increase in pertussis notifications in 2012, resulting in 2 deaths of neonates between 0-2 months of age in the Netherlands and 5 deaths in the UK, it is advisable to start as early as possible with the primary series which most countries do at 2 months of age. The early start of the primary series is important to make the window of susceptibility of neonates as small as possible and there is evidence that already one dose provides some protection (24, 26, 93, 94). However, the protection provided by the reduced Scandinavian 3-5-12 schedule seems to be comparable to that induced by other 3+1 schedules and it has the advantage of less vaccine administrations. The hospital admissions in Denmark and the incidence numbers in Finland of neonates 0-2 months of age are similar to the numbers in the Netherlands (Qiushiu He and Frits Mooi, confidential personal communication), but postponing the start of the primary series from 2 to 3 months is not acceptable at this moment in the Netherlands as this may increase pertussis in the most susceptible age group.
Based on the reported number of non-vaccinated pertussis cases in the Netherlands (2006-2010), it is estimated that timely vaccination could have prevented 13-22% of the cases below the age of one year (assuming that the parents were willing to vaccinate). In this period an absolute number of 99 cases (<1 year) contracted pertussis from the 70th day of life without being vaccinated. Another 74 cases (<1 year) contracted pertussis between the 42nd and 70th day of life without being vaccinated (data not shown). The latter group could potentially have been vaccinated at the age of six to nine weeks.

#### 8.2.1.2 Spacing between the primary vaccination series

The time interval between the vaccinations of the primary series seems favourable towards a 2 months spacing as compared to a 1 month spacing although data are rather scarce and mainly limited to the pneumococcal conjugate vaccines (PCV). Similar immunogenicity levels were obtained after the first booster preceded by a 2-4 primary series compared with 2-3-4 for PCV9 (95) and PCV7 (96, 97). A 2-3 schedule for PCV7 turned to be poorly immunogenic compared with the 2-4 schedule and an interval of 8 weeks seemed required for good immunogenicity responses (98). In addition, in a schedule with 2 months spacing the possibility of interference, the modulation of the vaccine response resulting from concurrent or sequential administration of several distinct vaccines, is less as compared with 1 month spacing (99). Moreover, older age appears to improve antibody responses due to a more mature immune system in the slightly older young children (100). The extended 2-4-6 schedule ends 2 months later than the accelerated 2-3-4 schedule, which is beneficial for the vaccine response due to a further maturation of the immune system. The possible advantages and disadvantages of the main four primary schedules are summarised in table 4.

#### 8.2.1.3 Timing of the first booster

The first booster is essential because antibody levels wane rapidly after the primary series and cellular memory immunity might not yet have been established completely (101, 102). Removing the first booster seems not advisable as shown by the recent Australian epidemic (see hereunder, (93, 94)). The timing of the first booster, however, varies between 10 and 24 months in the different countries indicating some flexibility in the vaccination schedule at this point.

### 8.2.2 Preschool boosters

In 26 out of 32 European countries a preschool booster has been implemented varying from as early as 3 years (UK (first booster) and Croatia) up to 7 years of age. In eight European countries a (pre)adolescent booster is implemented starting at 10 up to 17 years of age. Interestingly, two of these countries lack a preschool booster in their schedule (Austria and France).
The preschool booster has proven to be essential in providing protection in childhood, which has been shown in the Netherlands (103). The introduction of that booster in the end of 2001 at 4 years of age resulted in a shift of the peak incidence of whooping cough from children 4-5 years of age in 2001 up to 12-13 years in 2011. Recently, however, also increased notifications were observed in children 8-9 years of age. However, it should be noted that these children have been primed with a relative weak whole cell vaccine and careful monitoring the coming years is of utmost importance.
The timing of the preschool booster varies from three to seven years of age between the different countries, although it has been shown that antibody levels have waned to minimal concentrations already

in the 3rd year of life (5, 101). Nevertheless, the presence of memory B-cells specific for pertussis could be established in these children with (very) low antibody concentrations, suggesting protection on basis of the presence of cellular immunity. It remains to be investigated how well and how long this memory immunity actually protects the children. Epidemiological data from Sweden showed that the preschool booster should be given at 5-6 years after their primary schedule (3-5-12) in the current pertussis situation in Sweden. (104). An exact time point for the preschool booster is difficult to determine but it seems that postponing the vaccination from four to six years should be investigated, keeping in mind the role of siblings in transmitting pertussis to the newborn baby.

### 8.2.3 Outside Europe

The USA, Canada and Australia use a 2-4-6 schedule as primary series followed by an early booster (15-18 months), a preschool booster (4-6 years) and an adolescent booster (12-18 years). In Japan, a 3-4-6 primary schedule is used followed only by a booster between 18-24 months. Remarkably, in the USA despite their comprehensive vaccination schedule, whooping cough has re-emerged in the last decade resulting in 2010 in California in the largest pertussis epidemic since implementation of vaccination with 10 deaths of neonates (4). This indicates that even the most extensive schedule does not offer enough protection to the population against pertussis and emphasizes the need for better vaccines. In response to this re-emergence, CDC has advised maternal immunisation (105). Importantly, in 2003, Australia removed the first booster at 18 months from their schedule and in the last years a record pertussis epidemic was observed with increasing incidences in the younger age cohorts (three to four years) but also in older children (five to fourteen years) despite the preschool booster (93, 94).

## 8.3 Cost-effectiveness

Not applicable. (Obviously 3+1 is more expensive than 2+1.)

## 8.4 Feasibility and operational aspects

Changes in the vaccination schedule are in principle feasible. However, because delivery of vaccination is embedded in child health care with fixed contact moments, there may be some impediments to overcome.

**Table 4** Pertussis vaccination schedules.

| Schedule | Timing | Possible Advantage | Possible Disadvantage |
|---|---|---|---|
| Primary series | 2-3-4 months | Early protection | Possible interference<br>More vaccinations<br>Vaccinations at young age and less persistent immunity |
| | 2-4-6 months | Early protection,<br>Less interference,<br>Later age and more persistent immunity | More vaccinations |
| | 3-5 months | Less interference,<br>Later age and more persistent immunity<br>Less vaccinations | Later protection |
| | 2-4 months | Early protection,<br>Less vaccinations | Vaccinations at young age and less persistent immunity |
| First booster | 10-24 months | Effective | |
| Preschool booster | 3-7 years | Effective | Possible side effects |

### 8.5 Known unknowns

- A comparison of the efficacy of different schedules in countries, based on (e.g.) pertussis notifications in infants 0-4 months old.
- Long-term efficacy of different pertussis vaccines and vaccination schedules.
- Optimal spacing with respect to pertussis immunogenicity and side effects.

### 8.6 Summary

The current pertussis situation in the Netherlands should be a good reason to discuss the optimisation of the vaccination schedule during childhood. A reduction of the primary series from 3+1 to 2+1 schedule for the DTaP-IPV-Hib-HepB combination vaccine seems possible considering the immunogenicity and effectiveness of the vaccine components and the vaccine induced herd immunity with the exception of pertussis. As delaying the first vaccination may increase pertussis in infants, the current pertussis situation leaves only the possibility to change the accelerated 2-3-4 schedule to a reduced 3-5 schedule preceded by a pertussis vaccination at 2 months (2-3-5 schedule, see PIM study) or the mostly used 2-4-6 schedule with a probable benefit of the induction of a more persistent immunity.
Postponing the first booster from 11 months to 12-18 months and the preschool booster from 4 to 6 years seems logical in terms immunogenicity data induced by these acellular high-dose vaccinations and the experience abroad (used in most European countries, USA and Canada) and may improve long term immunity during childhood/adolescence in the Netherlands. However, these changes will require substantial changes in the logistics of the vaccination programme.

## 9 Cost-effectiveness studies

It is clear that, for recommendations in the context of collective prevention, the cost-effectiveness is an important issue. Following the short discussion for each scenario separately above, we make some general remarks on this subject.

Cost-effectiveness analyses report the results as the ratio between the cost of intervention and the saved costs of treatment due to averted infections, divided by the gain in quality adjusted life year (QALY) due to the averted infection, i.e. cost (€)/QALY gained. For a number of the vaccination strategies discussed here cost-effectiveness analyses have been performed. A couple of studies were focused on the Dutch situation (28, 90, 92). Furthermore, CIb has estimated cost-effectiveness regarding the vaccination strategies: neonatal, maternal and cocooning. Even though there is no official threshold in the Netherlands for when an intervention is regarded cost-effective, an often used threshold is €20,000 per QALY gained. This means that if the cost-effectiveness ratio is below this amount, it is regarded to be cost-effective. The cost-effectiveness ratios presented here include health care costs; estimates of production losses are not included nor discussed in this document.

In general, results from cost-effectiveness analyses are only valid under the assumptions and circumstances in which they are performed. This means that, for instance, country specific age-dependent incidence of disease, and country specific costs and health care structure affect the results. As a consequence, if an intervention is shown to be cost-effective in one country (e.g. Germany), it does not mean that it will be in another country (e.g. the Netherlands).

Even within one country there may be large differences in results between two cost-effectiveness studies. E.g. large differences were observed between two Dutch studies performed by CIb and Westra et al. (28). These differences are mainly explained by the assumptions made about under-reporting of pertussis (100 vs 200) and the length of the disease (6 weeks vs 3 months), and to some extent the severity. Sensitivity analyses of the two studies show that when these assumptions are similar, the estimations of the cost-effectiveness are also similar.

Preliminary further adjustments of the CIb analysis, calculating with the high incidence figures seen in the early months of 2012, show quite different cost-effectiveness ratios: neonatal vaccination about €180,000/QALY gained; parental (mother) vaccination about €75,000/QALY gained; and maternal vaccination about €50,000/QALY gained. The new estimates assume that the recent increase of disease persists a number of years, that only one in 100 cases is being notified, and that 2 deaths in infants would be prevented yearly.
The relative number of infants younger than one month registered is larger in 2012 compared to earlier years, which also contributes to a larger effect of the vaccination strategies.

In cost-effectiveness analyses, the herd immunity effects are of great importance, since all costs and effects should be taken into account. In the calculations of the cost-effectiveness of the strategies cocooning and maternal vaccination, the reduction in infant pertussis is actually the result of a herd immunity effect: the infant is protected due to less transmission from the mother.
One could speculate that if the mother is vaccinated transmission would be reduced also to other family members and close contacts, not only to the newborn. This would increase the gain in quality adjusted life years, making an intervention somewhat more cost-effective, but how much is difficult to say.

The estimates of the cost-effectiveness has shown to be quite sensitive to the assumptions about the severity of disease and the actual size of under-reporting.

A recent study modelling the cost-effectiveness of vaccination of one cohort of adolescents in the Netherlands results in an attractive cost-effectiveness ratio (90). These estimations are based on an under-reporting of more than 600 times, using notification data from the time before the pre-school booster vaccination, which was introduced in 2001. This might lead to an over estimation of the effect of vaccinating adolescents. The results presented in this study did not say anything about any potential effect on transmission to newborns.

Another Dutch study on the cost-effectiveness of a booster vaccination in 12-year olds, did include the indirect effect by using a dynamic model. The booster would be cost-effective and would reduce primary infection in infants, but would lead to an increase in ages >20. The results were sensitive to the assumptions made about length of immunity and the disease burden in adults, and based on a under reporting of 660 times the notified cases (92). Again, these results stress that more reliable data on disease burden in adults is needed.

## 10 Vaccination on an individual basis

Although not the objective of our analysis, a few remarks will be made on pertussis vaccination with the aim of individual protection.
People could choose to bring their protection against pertussis up to standard by having a booster vaccination, either to contribute to the protection of newborns in their surroundings (e.g. grandparents) or to escape from an exhausting period of long-lasting severe coughs (when they happened to see such a case in their surroundings).

In the Netherlands, so far, there are no clear guidelines nor a dedicated organisation for vaccinations apart from the NIP, except the National Programme for Flu Prevention carried out by the general practitioners and vaccinations at travel clinics. Therefore, at the Ministry of Health a policy to deliver safe and effective vaccines on an individual basis to those who may benefit from it, is being developed. These vaccinations could be delivered through primary care. Then guidelines should be available enabling the GP to counsel patients on the desirability and usefulness of certain vaccinations as well as rules for payment, as vaccination by the general practitioners is not covered by most health insurances. Otherwise, vaccination at the PHS travel clinics where the vaccines and the expertise are available, could be considered. At least it could be recommended to use DTaP-IPV vaccine instead of DT-IPV vaccine for people who get a booster vaccination for reasons of travel anyway.
Vaccination at travel clinics is at the person's own expense (sometimes covered by additional insurance policies, paid).

## 11 Improvement of pertussis vaccines

We have proposed that the resurgence of pertussis is the compound effect of pathogen adaptation and waning immunity and that the removal by vaccination of naïve infants as the major source for transmission was the crucial event which has driven the adaptions in *B.pertussis* populations (106). This shift in the ecology of *B.pertussis* has selected for strains which are more efficiently transmitted by primed hosts in which immunity has waned. The adaptation of *B.pertussis* to primed hosts involved delaying an effective immune response by antigenic divergence with vaccine strains, by increasing pertussis toxin production and by shutting down genes coding for antigens present in vaccines.

Antigenic divergence between vaccine strains and circulating strains has been observed with four of the five antigens included in current acellular vaccines: serotype 2, fimbriae, serotype 3 fimbriae, pertussis toxin and pertactin (106). Studies in mice have provided evidence that variation in in these antigens affects vaccine efficacy (see references in (106)). The second adaptation observed in *B.pertussis* populations involves the emergence of strains with increased pertussis toxin production (107). These so called P3 strains have gradually replaced the resident strains in the 1990s in Europe, the US and Australia (107-112). Indeed, there is evidence that this is a global phenomenon which has occurred in a period of 20-30 years (manuscript in preparation). Of particular significance is the close relationship between the emergence of the P3 strains and increased pertussis notifications in The Netherlands, Finland, Belgium and Australia (107, 111), (unpublished data). The third adaptation occurred most recently and involves the inactivation of *B.pertussis* genes coding for proteins used in pertussis vaccines, in particular pertactin (113-115) (our unpublished data).

Adaptations reveal weak spots in the pathogen’s defence and therefore suggest ways to improve vaccines (116). Pertussis vaccines should be "updated" to include protein antigen variants which predominate in current populations. The emergence and global spread of P3 strains underline the importance of pertussis toxin antibodies in controlling pertussis. Unfortunately, pertussis toxin antibodies wane relatively fast (101). To increase the persistence of pertussis toxin antibodies, chemically detoxified pertussis toxin should be replaced by pertussis toxin which has been genetically detoxified (117). Formaldehyde treatment of pertussis toxin has been shown to constrain antigen presentation to T cells and chemical detoxification has a significant effect on protein structure and may destroy protective epitopes (118). Further, compared to chemically detoxified pertussis toxin, genetically detoxified toxin is more immunogenic in humans (119,120).

A new, promising, approach to improve immunity against pertussis is the development of a live vaccine based on an attenuated *B.pertussis.* (121). The intranasally applied vaccine is undergoing phase I clinical trials. Evidence from the field suggests that immunity induced after infection lasts longer than immunity induced after vaccination (122) and indeed mice experiments showed that immunity induced by the live pertussis vaccine persists longer compared to acellular vaccines (123). Further, the live vaccine seems to induce a broader immunity as, in contrast to acellular vaccines, it also protects against *B. parapertussis* in mice (124). A live pertussis vaccine may be used for neonatal vaccination, although safety issues need to be addressed first. In addition, live vaccine may be used for adolescent and adult boosters, or during outbreaks. Apart from safety issues (e.g. safety in immune-compromised hosts), one question which should be resolved is how fast protective immunity is induced by the live vaccine.

## 12 International aspects

A resurgence of pertussis has been observed in many developed countries, including the UK and US (1, 4). Both countries have responded in several ways. The Joint Committee of Vaccination and Immunisation for England and Wales is studying the effects of different interventions, including a booster dose in teenagers and vaccinating pregnant women, healthcare workers, neonates, or close contacts of neonates (1). In the US, the Advisory Committee on Immunization Practices (ACIP) has updated recommendations for use of acellular pertussis vaccine (TdaP) in pregnant women and persons who have close contact with an infant aged <12 months. The US recently became the first country to recommend vaccination during pregnancy to provide immunity to both mother and baby. The CDC has initiated a study to conduct enhanced (strain) surveillance of pertussis and other *Bordetella* species (125). Studies evaluating TdaP effectiveness and duration of protection in adolescents fully vaccinated with DTaP are being conducted in Washington and California (125). Public awareness efforts have focused on informing residents about the signs and symptoms of pertussis and vaccination recommendations.

## 13 Epilogue

Before childhood vaccination was introduced in the 1950s, pertussis was a major cause of infant death worldwide (126). Although widespread vaccination of children significantly reduced pertussis morbidity and mortality, globally, pertussis still ranks 5th in child mortality caused by vaccine-preventable diseases. (127) Further, the number of countries in which pertussis has resurged is worrying and includes Norway (89), UK (1), Ireland (128), Israel (129), USA (http://www.cdc.gov/pertussis/surv-reporting.html), Canada (130), Australia (131) and New Zealand (132). Importantly, there is no evidence that equilibrium in pertussis epidemiology has been reached and in most countries a continuous trend upwards is seen. Finally, the fact that up to six vaccinations (e.g. in the US) are not able to curb the increase in pertussis, may have a significant impact on trust in the NIP and play into the hands of the anti-vaccine movement. The resurgence of pertussis and particularly the increasing incidence in infants represent an urgent public health problem. We believe that there are both practical and moral arguments for measures to reduce the incidence of pertussis in infants. In this document several scenarios are discussed which aim to reduce the pertussis burden in infants in the Netherlands. Whether or not the scenarios are cost-effective depends on many estimates and uncertainties and cost-effectiveness studies are probably most useful for mutual comparison of different scenarios.

The Dutch Health Council developed a framework to evaluate new vaccines for inclusion in the National Immunisation Programme (133, 134). It refers to the seriousness and extent of the disease burden, the effectiveness of the vaccination for the prevention of disease or the reduction of symptoms, the attainability of sufficient vaccine coverage, the safety of the vaccine, the acceptability of the vaccination, the cost-effectiveness of the vaccination and the priority, i.e. whether of the vaccination serves an urgent or potentially urgent public health need. The seriousness and extent of the disease as well as the priority have been dealt with above and are not discriminative for the possible vaccination scenarios. In table 5 we rank the different scenarios for the other criteria.

**Table 5** Ranking of different pertussis vaccination scenarios according to several criteria.

| scenario | effectiveness[&] | attainability | safety | acceptability for target population | cost-effectiveness |
|---|---|---|---|---|---|
| neonatal | ++ | +++ | +[#] | + | - |
| maternal | +++ | +++ | mother +++<br>child +++ | + | ± |
| cocooning | | | | | |
| mothers | ++ | ++ | +++ | +++ | ± |
| fathers | ++ | ± | +++ | +++ | - |
| HCW | ++ | ++ | +++ | ± | - |
| preconception | + | - | +++ | +++ | - |
| older children | - | +++ | +++ | ++ | - |
| adolescents | - | +++ | +++ | + | - |

[#] reactogenicity low; some concerns on long-term effects: with respect to Th1/Th2 balance
[&] Effectiveness in preventing pertussis in infants
Abbreviation: HCW, health care worker.

In our view maternal immunisation could be a feasible and focused approach with a potential high impact on pertussis morbidity and mortality in infants.

We emphasise the need for improved vaccines and continuing surveillance. Pathogens are moving targets (135) which may adapt quickly to human intervention, as is exemplified by the emergence of antibiotic resistant strains. The emergence of "vaccine-resistance" is a relative new phenomenon for bacterial pathogens, although extensively documented for the faster evolving viruses. Indeed, new influenza vaccines are introduced every year. In contrast, the development and introduction of bacterial vaccines may take up to 10 years. Clearly, there is an urgent need to speed up this process. For pertussis vaccines, relatively minor changes may suffice to significantly increase vaccine effectiveness. Maternal and neonatal pertussis immunisation and consequent adaptations of the vaccination schedule deserve further study including assessment of disease burden in adults. Studies are also needed on the acceptance of vaccination by the target group before any change in vaccination policy is implemented. Strain surveillance should be continued. Since mutations in *B.pertussis* may lead to costly changes in vaccines and vaccine schedules, it is important to substantiate the relevance of these mutations in in vitro and in animal models. Finally, the elucidation of the causes for resurgence of pertussis in the Netherlands, underlines the importance of an integrated approach to evaluate the NIP, involving clinical surveillance, immunosurveillance and strain surveillance.

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**Addendum**

Overzicht van in Nederland geregistreerde kinkhoestvaccins. Marianne de Bruijn
Bronnen: College Beoordeling Geneesmiddelen (www.cbg-meb.nl) en European Medicines Agency (http://www.ema.europa.eu)

| Product naam | Indicatie | Kinkhoest componenten | Registratiehouder |
|---|---|---|---|
| Infanrix hexa<br><br>DaKTP-Hib-HepB<br>DTPa-IPV-Hib-HBV | Primaire vaccinaties vanaf 2 maanden met een min interval van 1 maand. Het schema 6, 10 en 14 weken mag alleen worden gebruikt als bij de geboorte een dosis hepatitis-B-vaccin is gegeven!<br>Booster vaccinatie op ≥ 6 maanden na 2 primaire (11-13 maanden) en ≥ 6 maanden na 3 primaire vaccinaties (voorkeur <18 maanden).<br>De veiligheid en werkzaamheid van Infanrix hexa bij kinderen ouder dan 36 maanden is niet vastgesteld. | Acellulair<br><br>Pertussis toxoid 25 mcg<br>Filamentous Haemagglutinin 25 mcg<br>Pertactin 8 mcg | GlaxoSmithKline Biologicals S.A., BE |
| Infanrix Penta<br><br>DaKTP-HepB DTPa-IPV-HBV | Primaire vaccinaties vanaf 2 maanden met een min interval van 1 maand. Het schema 6, 10 en 14 weken mag alleen worden gebruikt als bij de geboorte een dosis hepatitis-B-vaccin is gegeven!<br>Booster vaccinatie op ≥ 6 maanden na 2 primaire (11-13 maanden) en ≥ 6 maanden na 3 primaire vaccinaties (voorkeur <18 maanden).<br>De veiligheid en werkzaamheid van Infanrix penta bij kinderen ouder dan 36 maanden is niet vastgesteld. | Acellulair<br><br>Pertussis toxoid 25 mcg, Filamentous Haemagglutinin 25 mcg, Pertactin 8 mcg | GlaxoSmithKline Biologicals S.A., BE |
| Infanrix-IPV-Hib<br><br>DaKTP-Hib DTPa-IPV-Hib | Primaire vaccinatieschema met drie doses met een min interval van 1 maand (zoals op de leeftijd van 2, 3, 4 maanden; 3, 4, 5 maanden; 2, 4, 6 maanden; 3, 5, 11 of 12 maanden).<br><br>Booster vaccinatie volgens officiële richtlijnen<br>De veiligheid en werkzaamheid van Infanrix-IPV-Hib bij kinderen ouder dan 36 maanden is niet vastgesteld. | Acellulair<br><br>Pertussis toxoïd 25 mcg<br>Filamenteus hemagglutinine 25 mcg<br>Pertactine 8 mcg | GlaxoSmithKline Biologicals, Zeist, NL |

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| Infanrix-IPV<br><br>DaKTP<br>DTaP-IPV | Primaire vaccinatieschema met drie doses met een min interval van 1 maand (zoals op de leeftijd van 2, 3, 4 maanden; 3, 4, 5 maanden; 2, 4, 6 maanden; 3, 5, 11 of 12 maanden).<br><br>Booster vaccinatie volgens officiële richtlijnen.<br><br>Alleen vermelding dat het niet bedoeld is voor volwassenen. Vermelding hoofdpijn als bijwerking boostervaccinatie op 6-13 jaar.. | Acellulair<br><br>Pertussis toxoïd 25 mcg<br>Filamenteus hemagglutinine 25 mcg<br>Pertactine 8 mcg | GlaxoSmithKline Biologicals, Zeist, NL |
| Pediacel<br><br>DaKTP-Hib<br>DTPa-IPV-Hib | Primaire (2 of 3 vaccinaties met min. interval 1 maand) en boostervaccinatie (min interval 6 maanden na primaire serie) bij zuigelingen en kinderen vanaf de leeftijd van 6 weken tot de vierde verjaardag | Acellulair<br>Pertussistoxoïd (PT) 20 mcg, Filamenteus hemagglutinine (FHA) 20 mcg,<br>Pertactine (PRN) 3 mcg, Fimbriae type 2 en 3 (FIM) 5 mcg | Sanofi Pasteur MSD, BE |
| Tritanrix HepB<br><br>DwKT-HepB<br>DTPw-HBV | Primaire vaccinaties vanaf 6 weken.<br>Het primaire vaccinatieschema bestaat uit drie doses binnen de eerste zes levensmaanden met een min interval van 4 weken. Bij een 6-10-14 weken schema, wordt aanbevolen bij de geboorte een dosis HBV-vaccin te geven om de bescherming te verbeteren. Boosterdosis voor tweede levensjaar of volgens lokale richtlijnen.<br>Niet bestemd voor volwassenen | Whole cell<br><br>Bordetella pertussis (geïnactiveerd) ten minste 4 IE | GlaxoSmithKline Biologicals S.A. |
| Boostrix<br><br>dakT<br>dTap | Voor boostervaccinaties vanaf 4 jaar.<br>Boostrix moet worden toegediend volgens de officiële aanbevelingen en/of lokale voorschriften met betrekking tot het gebruik van vaccins met een lage dosis difterie-, tetanus- en pertussisantigenen.<br>Er zijn geen toereikende gegevens over het gebruik van Boostrix bij zwangere vrouwen en dierstudies naar reproductietoxiciteit zijn niet uitgevoerd. Zoals met andere geïnactiveerde vaccins, is niet te verwachten dat vaccinatie met Boostrix schadelijk is voor de foetus. Het effect van toediening van Boostrix bij vrouwen die borstvoeding geven is niet onderzocht. Echter, omdat Boostrix toxoïden of geïnactiveerde antigenen bevat, wordt geen risico | Acellulair<br><br>Pertussistoxoïd 8 mcg<br>Filamenteus Hemagglutinine 8 mcg<br>Pertactine 2,5 mcg | GlaxoSmithKline Biologicals, Zeist, NL |

| | | | |
|---|---|---|---|
| | verwacht voor de zuigeling. | | |
| Boostrix Polio<br><br>dakTP<br>dTap-IPV | Voor boostervaccinaties vanaf 4 jaar.<br>Boostrix Polio moet worden toegediend volgens de officiële aanbevelingen en/of lokale voorschriften met betrekking tot het gebruik van vaccins met een lage dosis difterie-, tetanus- en pertussisantigenen<br>combinatie met poliomyelitisantigenen.<br>Gegevens over het effect op vruchtbaarheid zijn niet bekend. Het effect van Boostrix Polio op de embryo-foetale ontwikkeling is niet vastgesteld. Er zijn geen teratogene effecten waargenomen na toediening van vaccins die difterie- of tetanustoxoïden, of geïnactiveerd poliovirus bevatten aan zwangere vrouwen.Het gebruik van dit gecombineerde vaccin wordt niet aanbevolen tijdens de zwangerschap.<br>Het effect van toediening van Boostrix Polio bij vrouwen die borstvoeding geven is niet onderzocht. Echter, omdat Boostrix Polio toxoïden of geïnactiveerde antigenen bevat, wordt geen risico verwacht voor de zuigeling. | Acellulair<br><br>Pertussistoxoïd 8 mcg<br>Filamenteus Hemagglutinine 8 mcg<br>Pertactine 2,5 mcg | GlaxoSmithKline Biologicals, Zeist, NL |
| Triaxis<br>dakT<br>dTap | Triaxis® is aangewezen voor de actieve immunisatie tegen tetanus, difterie en kinkhoest bij personen<br>vanaf de leeftijd van 4 jaar als booster na een primaire immunisatie.<br>Het gebruik van Triaxis® dient te gebeuren op basis van officiële aanbevelingen.<br><br>Gegevens bij een beperkt aantal zwangerschappen na vaccinatie wijzen niet op bijwerkingen van<br>Triaxis® op de zwangerschap of de gezondheid van de foetus/pasgeboren baby. Tot op heden zijn<br>geen andere relevante epidemiologische gegevens beschikbaar. De resultaten van dieronderzoek<br>duiden niet op directe of indirecte schadelijke effecten wat betreft zwangerschap, embryonale/foetale<br>ontwikkeling, bevalling of postnatale ontwikkeling. Het effect op zuigelingen die borstvoeding krijgen van een moeder die met Triaxis® werd gevaccineerd, is echter niet | Acellulair<br><br>Kinkhoestanatoxine 2,5 mcg<br>Filamenteus hemagglutinine 5 mcg<br>Pertactine 3 mcg<br>Fimbriale agglutinogenen types 2 en 3: 5 mcg | Sanofi Pasteur MSD, BE |

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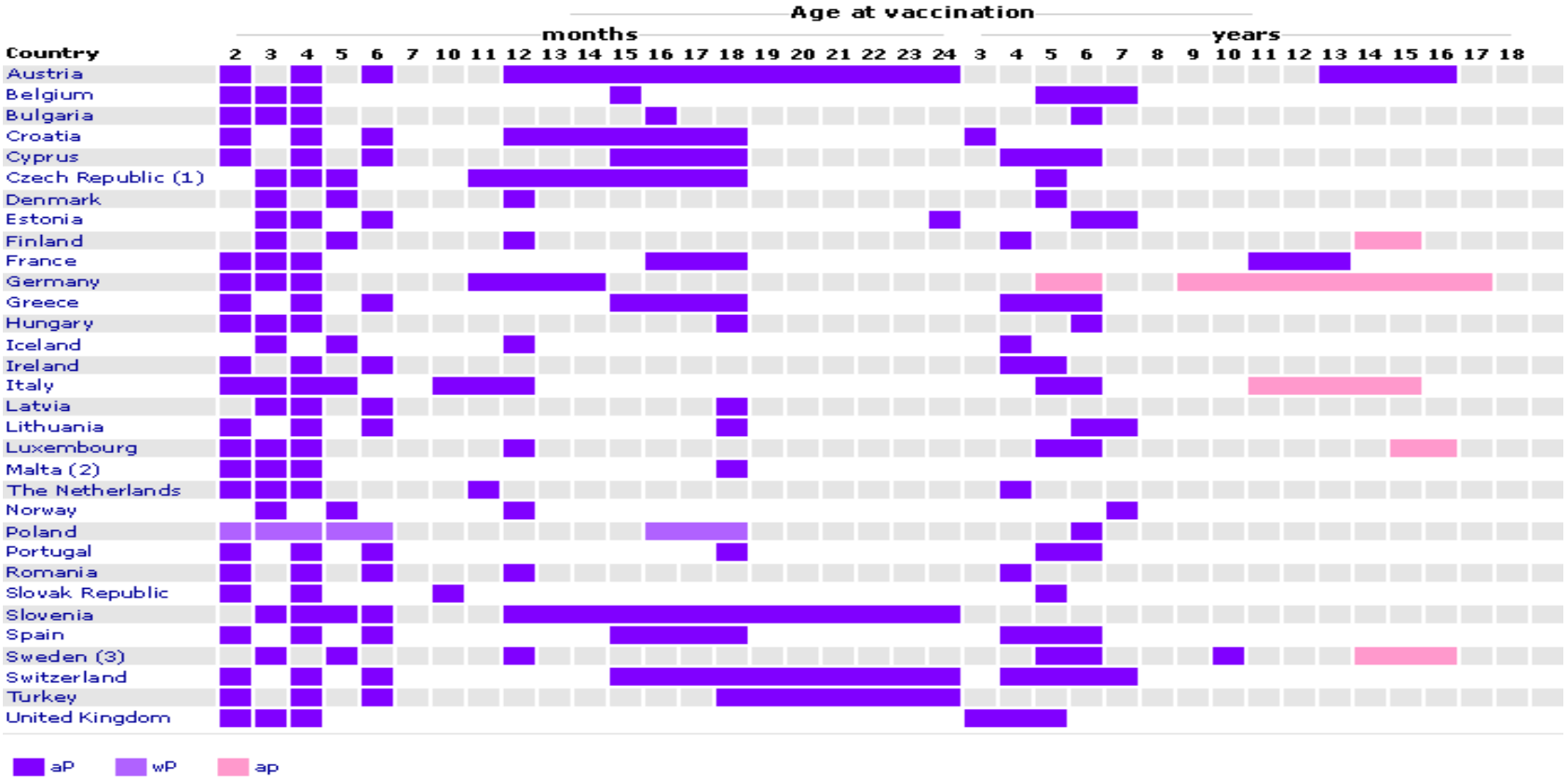
| | bestudeerd. | | |
| Triaxis Polio<br><br>daKTP<br>dTaP-IPV | Alleen geregistreerd voor eenmalige booster vaccinatie na primaire serie<br><br>Niet geregistreerd voor kinderen < 3 jaar<br><br>Kinderen vanaf 3 jaar en adolescenten moeten zelfde dosis krijgen als volwassenen<br>Het effect van TRIAXIS POLIO op de embryo-foetale ontwikkeling werd niet geëvalueerd. Er is een beperkte hoeveelheid postmarketinginformatie beschikbaar over de veiligheid van het toedienen van TRIAXIS POLIO aan zwangere vrouwen. Het gebruik van dit gecombineerd vaccin tijdens de zwangerschap wordt niet aanbevolen. Het effect van toediening van TRIAXIS POLIO tijdens de borstvoeding werd nog niet geëvalueerd. | Acellulair Kinkhoesttoxoïd: 2,5 mcg, Filamenteus hemagglutinine, 5 mcg, Pertactine 3 mcg, Fimbriale agglutinogenen 2 + 3, 5 mcg | Sanofi Pasteur MSD, BE |

Vaccination schedules in European countries. Source: EUVAC.NET:
http://www.euvac.net/graphics/euvac/vaccination/vaccination.html




N.B. Unless otherwise stated in the footnotes below, each coloured box represents one dose of pertussis vaccine.
(1) The primary course of 3 doses is recommended at 13 weeks, 17 weeks-1 year and 21 weeks-1 year of age. Booster doses are recommended at 11 months 1 week-18 months of age and at 5 years of age.
(2) First dose given at 6 month of age.
(3) Children born before 2002 are boosted at 10 y, children born in 2002 and later at ages 5-6 and 14-16 years.
http://www.cdc.gov/pertussis/surv-reporting.html

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