Epidemiology of pertussis in the Netherlands and implications for future vaccination strategies

degreeff, S.C.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
The case for maternal vaccination against pertussis

Frits R. Mooi
Sabine C. de Greeff

Lancet Infect Dis 2007;7:614-624
Abstract
Despite high vaccine coverage pertussis is increasing in a number of countries. Particularly alarming is the increase of pertussis in infants too young to be (fully) vaccinated, because the highest morbidity and mortality is observed in this category. Maternal vaccination offers the possibility to protect infants from birth until immunity is induced by active vaccination and has been shown to be effective and safe for tetanus over long periods of time. Maternal vaccination studies with whole-cell pertussis vaccines have not shown serious adverse effects in mother and child. In one study, protection of newborn babies was found. Additional support for the efficacy of maternal vaccination comes from studies showing that transfer of antibodies confers protection against pertussis. Maternal vaccination might be an effective way to decrease morbidity and mortality caused by pertussis in newborn babies.
Introduction

Although pertussis vaccines have been used in many countries since the 1940s and 1950s, the disease has remained endemic. Furthermore, in the 1980s and 1990s, a resurgence of pertussis was observed in a number of countries despite high vaccination coverage [1-5]. Several explanations have been put forward for this phenomenon including improved surveillance, waning immunity, bacterial evolution and the use of subpotent vaccines [6]. The relevance of these factors in the resurgence of pertussis might differ between countries - for example, the use of a subpotent vaccine had an important role in Canada, whereas both a subpotent vaccine and strain evolution were important in the Netherlands [1, 3]. The resurgence of pertussis has resulted in an increased morbidity and mortality in infants too young to be vaccinated. In several European countries, infants obtain their primary vaccination at the ages of 2, 3, and 4 months [7]. Australia, Canada, and the USA follow a schedule of primary vaccination with doses at 2, 4, and 6 months. Assuming that acceptable immunity is reached 1 month after the third injection [8], this leaves infants younger than 5-7 months at least partially susceptible to pertussis. It is in this age category that the highest morbidity and mortality is observed [9].

Morbidity and mortality in infants caused by pertussis

In the Netherlands, 416 out of 756 (55%) infants less than 6 months of age and reported with pertussis were hospitalised in 2000-04. In the past decade, nine deaths caused by pertussis were registered in the Netherlands, all in children younger than 3 months of age. In the USA, 1567 out of 2488 (63%) infants less than 12 months of age reported with pertussis were hospitalised in 2000-04 [10]. Of the 100 pertussis-related deaths reported in the USA in this period, 90 (90%) were in infants aged less than 4 months and 76 (76%) were in infants aged less than 2 months [10]. Also, in the UK the morbidity of reported pertussis is highest among infants less than 2 months of age [11].

Despite high vaccination rates, the incidence of reported pertussis in infants younger than 12 months of age in the USA increased by 49%, from 34.2 per 100,000 population in the 1980s to 51.1 per 100,000 population in the 1990s. This increase was predominantly caused by the increase of disease in infants less than 4 months of age [12]. Increasing rates of infant pertussis have also been documented in Canada and several European countries [13, 14]. Moreover, the number of deaths caused by pertussis in infants younger than 4 months of age is also increasing.

One study showed that the reported number of deaths caused by pertussis in this age group in 1980-1989 and 1990-1999 in the USA were 49 and 84, respectively, an increase of 71% [15]. In line with the observations in the USA, the incidence of pertussis in infants in the Netherlands
increased 2.8-fold in the period 1996-2004 compared with 1989-95. The incidence of hospitalisations in infants increased by 82%, from 66.3 per 100,000 population in the period 1989-1995 to 121.0 per 100,000 population in 1996-2004 (Table 1) [1, 16]. The number of deaths in the two periods was two and nine, respectively. All deaths occurred in infants less than 3 months of age, except for one death in 1993 in the 5-9-year age group. Since routine vaccination is scheduled at 2, 3, and 4 months in the Netherlands, most of these children were too young to be protected directly by vaccination.

Presumably, the number of infant cases of pertussis is higher than routine surveillance data report because pertussis in infants might be atypical and therefore not recognized [9, 17, 18]. A case report from the UK demonstrated that out of five infants less than 3 months old who were admitted to hospital for pertussis, none showed the characteristic whoop or paroxysmal cough, and one of the infants did not cough at all [19]. Application of the capture-recapture method to assess the completeness of reporting to the national surveillance system in the USA indicated that more than two-thirds of all pertussis deaths were not accounted for in the national disease reporting system [20]. A similar study in the UK concluded that mortality of pertussis in infants is underestimated by 60% in the national death register [21]. Another study in the UK showed that morbidity in infants was also underestimated: pertussis was clinically suspected on admission in only 28% of the infants who were later diagnosed with the disease [22].

Table 1. Incidence of hospitalisations per 100,000 for pertussis by age group in the Netherlands in 1989-1995 compared with 1996-2004.*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 years</td>
<td>66.3</td>
<td>121.0</td>
<td>1.8</td>
</tr>
<tr>
<td>1-4 years</td>
<td>4.9</td>
<td>6.8</td>
<td>1.4</td>
</tr>
<tr>
<td>5-9 years</td>
<td>1.3</td>
<td>2.59</td>
<td>2.0</td>
</tr>
<tr>
<td>10-14 years</td>
<td>0.4</td>
<td>0.54</td>
<td>1.4</td>
</tr>
<tr>
<td>15-19 years</td>
<td>0.03</td>
<td>0.09</td>
<td>3.0</td>
</tr>
<tr>
<td>More than 19 years</td>
<td>0.02</td>
<td>0.07</td>
<td>3.5</td>
</tr>
<tr>
<td>All ages</td>
<td>1.21</td>
<td>2.2</td>
<td>1.8</td>
</tr>
</tbody>
</table>

* The incidence for both periods (1989-1995 and 1996-2004) was calculated as (number of hospitalised cases in the concerning period × 100,000)/population at risk in that period. Data taken from references [1] and [16].
Vaccination strategies to reduce pertussis in infants

Different vaccination strategies can be implemented to protect infants against pertussis. Protection of unvaccinated or partly vaccinated infants can be enhanced, indirectly, by decreasing the circulation of *Bordetella pertussis*. Universal vaccination of 4-year-olds, adolescents, adults, or selective immunization of new mothers and fathers (cocooning) not only protects the vaccinated group, but increases herd immunity and hence reduces disease transmission to unvaccinated or incompletely vaccinated infants. Several studies have provided evidence that this approach might be successful. The introduction of a booster vaccination for 4-year-old children in the Netherlands reduced the number of hospitalisations among infants less than 4 months of age [23]. In Canada, introduction of an adolescent booster vaccination not only resulted in a decrease in the pertussis incidence in this age group, but also in infants less than 12 months of age [24]. In Australia, a small decrease in hospitalisations in children aged 3-4 months was observed after the introduction of a booster given to children of 4 years of age. However, no change in the 0-2 month age group was reported [25, 26].

Direct protection of the infant may be conferred by maternal and neonatal vaccination. Compared with neonatal vaccination, maternal vaccination has several advantages. First, maternal vaccination offers the possibility to protect the infant from birth until immunity is achieved by active vaccination. By contrast, neonatal vaccination will leave the infant susceptible to pertussis for a period of weeks to months depending on how fast immunity is induced. An advantage of both maternal and neonatal vaccination is the accessibility of the targeted group, since both (pregnant) mothers and infants frequently visit health-care centres.

Maternal immunity

Maternal vaccination confers protection by efficient placental transfer of maternal antibodies [27, 28]. Maternal memory T cells and B cells are ineffective because of differences in tissue antigens (HLA in particular) between the mother and her foetus [27]. Furthermore, there is no evidence that immune cells are able to cross the placental barrier and establish themselves in the foetus. The time period in which maternal vaccination is effective depends on the timing of the mother’s immune response to the vaccine, and also the timing of maternal-foetal IgG transport [29, 30]. Foetal IgG remains low until the second trimester and increases during the third trimester. Indeed, the rate of increase in foetal IgG concentration between 29 and 41 weeks of gestation is roughly twice that seen between 17 and 28 weeks [31]. For these reasons, and also in view of real or apparent side-effects, the optimum timing for maternal vaccination is in the third trimester, probably between weeks 30 and 32 [28]. The IgG subclasses are transported with different efficiency according to the following sequence: IgG1 (most efficient), IgG4,
IgG3, IgG2 (least efficient) [31]. Thus it is important to determine the predominant antibody subclass induced by maternal vaccination, because this will determine the efficacy in the child. Since transmission of maternal antibodies reaches its maximum during the last few weeks of pregnancy, premature infants may be deficient in protective antibodies. However, maternal vaccination offers additional advantages for breastfed infants who passively acquire IgA antibodies from breast milk. Protection of infants in this manner has been demonstrated for both gastrointestinal and respiratory pathogens [32]. High IgA titres in sera from infants younger than 1 year of age were found to correlate with reduced duration of positive pertussis culture and PCR in throat samples [33]. These findings point to bactericidal effects of anti-B. pertussis IgA in human beings. Bactericidal effects of anti-B. pertussis IgA antibodies have been observed in transgenic mice [34].

Maternal vaccination

The usefulness of maternal vaccination was already recognized more than 120 years ago. In 1879, Burkhardt [35] reported that infants born to mothers who had “Jennerian vaccination” during pregnancy were protected from the vaccinia virus during the first days of life. In 1892, Ehrlich demonstrated the protective function of maternally transferred antibodies against microbial infections in mice offspring [36]. Furthermore, in the early 20th century it became clear that certain common infectious diseases such as diphtheria, poliomyelitis, scarlet fever, and measles did not manifest themselves in the first few months of life because of passively acquired antibodies from the immune mother [37, 38]. It was also noted in this period that other infectious diseases attack the neonate and young infant because they failed to acquire antibody from mothers, who had either no immunity or low levels of antibodies. More recent studies have confirmed these observations by showing that the occurrence of some neonatal infections - caused by group B streptococci, Haemophilus influenzae type b (Hib), and respiratory syncytial virus - is correlated with low maternal or neonatal antibody levels [39-41].

These insights stimulated attempts to protect newborn babies by maternal vaccination. For only a few diseases this has led to the incorporation of maternal vaccination in the routine vaccination programme, tetanus vaccination being the most prominent example [28, 42]. One of the reasons why maternal vaccination has not been implemented more widely is the initial success of infant vaccination, which has substantially reduced morbidity and mortality in childhood. More recently, liability issues have hampered the application of maternal vaccination [43].
It is noteworthy that the success of vaccination programmes has led to a reassessment of the usefulness of maternal vaccination. Because of mass vaccination, the circulation of many pathogens has decreased, leading to diminished population immunity as a result of lack of natural boosters. Consequently, most women in childbearing age now have low levels of antibodies against childhood diseases. Reduced levels of neutralizing antibodies during pregnancy influence the competence of transferred maternal immune protection, leading to a larger window of susceptibility in newborn babies. The latter could result in an increase of childhood infections and an exacerbation of infections that are usually mild. Currently, vaccines with the highest potential benefit in reducing childhood illness by maternal vaccination are those for respiratory syncytial virus, *Streptococcus pneumoniae*, group B streptococci, *B. pertussis*, and parainfluenza virus type 3 [28, 44].

**Transfer and persistence of maternal antibodies**

Preferably, maternal vaccination should completely close the window of susceptibility in the infant by providing immunity until this is replaced by active vaccination. A German study assessed the effectiveness of complete and partial pertussis vaccination for the prevention of severe pertussis requiring hospitalisation in 529 patients [8]. The vaccination schedule was 2, 3, and 4 months and for most doses (89%) a three-component acellular vaccine was used. Vaccine efficacy was 68%, 92%, and 100% for one, two, and three doses, respectively. Thus, ideally, maternal vaccination should provide protection until the third vaccination is given – i.e., during the first 4-5 months after birth.

In one study the average half-life of human maternal IgG1 was found to be 48.4 days in infants [45]. However, the persistence of protective levels of maternal antibodies differs widely depending on, for example, initial levels, specificity and avidity. Meningococcus type A or C and Hib antibodies remained at protective levels for 3 months and more than a year, respectively, after maternal vaccination [32]. The levels of *B. pertussis*-specific antibodies required for protection are not known. Active placental transfer of pertussis antibodies has been observed resulting in higher concentrations in the newborn baby compared with the mother [46]. Transplacental pertussis antibody concentrations in newborn babies were found to decline with a half-life of around 6 weeks and by the age of 2-6 months most infants had no detectable antibodies to *B. pertussis* [46-49].
Interference of maternal antibodies with vaccination of the child

A major concern associated with maternal vaccination is interference with the childhood vaccination, because pre-existing antibodies gained by placental transfer might affect the infant’s immune response to primary immunization. It is now assumed that the primary cause for maternal interference is epitope masking by maternal antibodies, preventing antigen binding by infant B cells [50]. The inhibitory effect is dependent on the ratio of maternal antibodies at the time of vaccination and the dose of antigen used to vaccinate the infant. Several studies have addressed the issue of maternal interference in pertussis vaccination. Maternally derived antibodies have been shown to interfere with antibody responses when whole-cell vaccines were used, but not, or much less, when acellular vaccines were used in the infant [48, 51, 52]. The latter can probably be attributed to the higher amounts of antigens present in acellular vaccines. However, in these studies the maternal population was immunized by infection or vaccination with a whole-cell vaccine and, since maternal immunization with acellular vaccines might induce higher levels of antibodies, it may show a higher degree of interference with infant immunization.

Evidence for maternal immunity against pertussis

Ethical, technical, and legal dilemmas complicate the possibility of undertaking efficacy trials, hence recent information on the efficacy of maternal vaccination and its possible risks is limited. Consequently, it is important to review the currently available evidence that maternal immunity is effective against pertussis in neonates. In the prevaccination era, it was common knowledge that, although newborn babies had a high degree of resistance to childhood diseases such as measles, poliomyelitis, scarlet fever, and diphtheria, they appeared to be susceptible to pertussis from the day of birth [37, 53]. This led to the idea that maternal immunity against pertussis was ineffective. However, sero-epidemiological studies in this period indicated that only 14-34% of the pregnant women had detectable antibodies to pertussis [54]. This suggests that the relative high incidence of pertussis in newborn babies compared with other childhood diseases is because of lack of booster infections of mothers, or because of the fact that immunity to pertussis wanes faster compared with other childhood diseases. In a recent study, lack of maternal antibodies has been proposed to be a risk factor for infant pertussis [55].
Role of antibodies in pertussis immunity

Maternal immunity is based on passively acquired antibodies [29], in particular IgG1 (see above); thus it is important to establish whether antibodies alone suffice for protection of the newborn against pertussis. There is ample evidence that this is the case, as discussed below.

Antibody titres against pertussis antigens are correlated with protection in human beings

Early studies indicated that, although immunity might exist in the absence of agglutinins (antibodies that agglutinate bacteria), susceptibility is not observed in the presence of high titres of agglutinins [56, 57]. During field trials with whole-cell vaccines in the UK in the 1950s, it was also shown that agglutinin titres correlated with protection against pertussis in children [58]. Later, it was shown that agglutinating antibodies are mainly directed against fimbriae [59]. More recently, levels of antibodies against filamentous haemagglutinin, pertussis toxin, pertactin, fimbriae, and lipopolysaccharide have been associated with protection against pertussis [60-66]. However, correlation does not imply causation, and the antibody titres against distinct antigens might reflect other immune mechanisms important for protection, such as memory and cellular immunity, or even an overall elevated antibody level against \textit{B. pertussis} antigens. Evidence for a direct role of antibodies in pertussis immunity has been obtained from passive vaccination studies in animals and human beings.

Passive vaccination studies in animals

Results from animal models used to study immunity to \textit{B. pertussis} should be interpreted carefully, because the disease differs substantially between animals and human beings. Nevertheless, important relations have been found between vaccine efficacies established in human beings and mice [58, 67, 68]. There is substantial evidence that transfer of antibodies can confer protection in animals (Table 2). The antibodies used for passive vaccination were raised against specific antigens, some of which are part of the current acellular vaccines (e.g., pertussis toxin, filamentous haemagglutinin, and pertactin), or whole bacteria. In mice, passive vaccination has been shown to reduce colonisation, loss in bodyweight, leucocytosis, and number of deaths. Particularly relevant are experiments performed by Huang and colleagues [69] in which monkeys were passively vaccinated with serum from infected or vaccinated monkeys. Three out of four monkeys treated with convalescent serum did not develop pertussis, whereas one out of two monkeys injected with serum from vaccinated monkeys developed disease. Control animals developed a disease very much like pertussis, except that whoops were absent.
Passive vaccination studies in human beings

Prophylactic and therapeutic treatment of pertussis by passive vaccination has a long history and the first attempts, often with a few infants, were made in the early 1900s [70, 71]. In 1923, Debré [72] passively vaccinated 40 children who had intimate contact with a child with pertussis. Of these 40 children, 31 did not develop pertussis, whereas six children had pertussis in an attenuated form. Three children developed normal pertussis. Many studies followed, which were summarised by Bradford in 1935 [73].

Table 2. Passive vaccination studies in animals.

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Source antibodies</th>
<th>Animal model</th>
<th>Challenge</th>
<th>Outcome$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al. (1962) [69]</td>
<td>Whole-cell vaccine</td>
<td>Monkey</td>
<td>Monkey</td>
<td>Aerosol</td>
</tr>
<tr>
<td>Sato et al. (1981) [120]</td>
<td>Filamentous haemagglutinin or pertussis toxin</td>
<td>Rabbit</td>
<td>Mouse</td>
<td>Aerosol</td>
</tr>
<tr>
<td>Sato et al. (1984) [121]</td>
<td>Pertussis toxin</td>
<td>Monoclonal antibody</td>
<td>Mouse</td>
<td>Intracerebral, aerosol</td>
</tr>
<tr>
<td>Sato and Sato (1985) [95]</td>
<td>Filamentous haemagglutinin or pertussis toxin</td>
<td>Mouse</td>
<td>Mouse</td>
<td>Aerosol</td>
</tr>
<tr>
<td>Oda et al. (1985) [122]</td>
<td>Diverse</td>
<td>Human colostrum</td>
<td>Mouse</td>
<td>Aerosol</td>
</tr>
<tr>
<td>Montanar et al. (1985) [123]</td>
<td>Pertactin$^b$</td>
<td>Monoclonal antibody</td>
<td>Mouse</td>
<td>Aerosol</td>
</tr>
<tr>
<td>Kinura et al. (1990) [124]</td>
<td>Filamentous haemagglutinin</td>
<td>Goat, rat</td>
<td>Mouse</td>
<td>Aerosol</td>
</tr>
<tr>
<td>Olander et al. (1990) [125]</td>
<td>Whole cells, filamentous haemagglutinin, pertussis toxin</td>
<td>Mouse</td>
<td>Mouse</td>
<td>Intranasal</td>
</tr>
<tr>
<td>Shahin et al. (1990) [126]</td>
<td>Pertactin</td>
<td>Monoclonal antibody</td>
<td>Mouse</td>
<td>Aerosol</td>
</tr>
<tr>
<td>King et al. (2001) [127]</td>
<td>Pertactin</td>
<td>Monoclonal antibody</td>
<td>Mouse</td>
<td>Intranasal</td>
</tr>
<tr>
<td>Hellwig et al. (2003) [128]</td>
<td>Whole-cell vaccine</td>
<td>Rabbit</td>
<td>Mouse</td>
<td>Intranasal</td>
</tr>
</tbody>
</table>

$^a$ Outcome of challenge in vaccinated animals, relative to control animals.
$^b$ Derived from Bordetella bronchiseptica. Challenge with a B. bronchiseptica strain.
$^c$ With B. bronchiseptica.
Bradford concluded “it seems probable that immune blood is effective in the prevention and modification of pertussis if given before the catarrhal symptoms appear. If given after the disease is established favourable results are less apparent”. Two important improvements in passive vaccination were the use of more defined, hyperimmune serum from recently vaccinated adults [74] and the lyophilisation of serum [75]. The latter allowed stable storage and to four-fold concentration of serum. In the period 1935-47, additional studies were carried out to assess the effect of passive vaccination against pertussis. Lack of (untreated) controls makes it difficult to interpret the results. Both promising [75-87] and negative [88-91] results were obtained with passive vaccination.

Different outcomes were caused by several factors. The potency of the sera used probably differed extensively – e.g., sera were used from adults without a known history of pertussis, adults whom had pertussis in childhood, and adults who had recent pertussis. The doses applied varied widely, from 10-140 mL. Importantly, infants were treated in different stages of the disease and the length and intensity of exposure after treatment was often not well defined. To correct for these factors, untreated controls are essential.

A number of studies in which infants were treated before any evidence of clinical disease and that included untreated controls are shown in Table 3. Compared with the untreated infants the efficacy of passive vaccination varied between -34% and 88%. Only one study did not find a positive effect of passive vaccination [89]. In this study, susceptibility for disease was assessed for 28 days after passive vaccination and it is conceivable that protection conferred by the passively acquired antibodies did not last that long.

In more recent times, Granstrom and colleagues [92] investigated the therapeutic effect of high titre, hyper-immune human serum raised with a monocomponent or a two-component acellular vaccine (with, respectively, pertussis toxin and pertussis toxin/filamentous haemagglutinin). The control consisted of a 20% albumin solution. The main finding was a significantly shorter duration of whoops in the treated group compared with the control group. Duration of whoops post-treatment was 8.7 days (95%CI: 4.8-12.6) in the 33 children receiving immunoglobulin versus 20.6 (95%CI: 11.9-29.3) in the 14 receiving placebo (P=0.0041). Early therapy was important, since the duration of whoops was shorter in children with less than 7 days' disease duration before treatment than in those with disease duration of 8-14 days. Passive vaccination did not decrease the duration of vomiting or coughs that were not followed by whooping.

Bruss and colleagues [93] investigated the therapeutic effect of a 4% IgG solution of pooled plasma from donors immunized with inactivated pertussis toxoid for passive vaccination of infants (26 patients, mean age 9.7 weeks). No control group was included. Improvements in paroxysmal coughing, desaturations, bradycardic episodes, and a decline in lymphocyte count
Table 3. Efficacy of passive vaccination in exposed infants.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Group size</th>
<th>Age (number)</th>
<th>Seruma</th>
<th>Volumeb</th>
<th>Injections</th>
<th>No disease</th>
<th>Disease</th>
<th>Efficacyc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradford (1935) [73]</td>
<td>27</td>
<td>0-3 yrs (24), &gt;3 yrs (3)</td>
<td>Normal adult and convalescent</td>
<td>6-10 mL</td>
<td>One</td>
<td>12 (44%)</td>
<td>15 (56%)</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>1-3 yrs (17)</td>
<td>Untreated</td>
<td>...</td>
<td>0</td>
<td>20 (100%)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Paterson et al. (1935) [80]</td>
<td>95</td>
<td>1 month to 4 yrs</td>
<td>Convalescent</td>
<td>10 mL</td>
<td>One</td>
<td>40 (42%)</td>
<td>55 (58%)</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>1 month to 4 yrs</td>
<td>Untreated</td>
<td>...</td>
<td>6 (11%)</td>
<td>49 (89%)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Meader (1937) [81]</td>
<td>115</td>
<td>0-6 yrs</td>
<td>Convalescent</td>
<td>10 mL</td>
<td>One</td>
<td>78 (67%)</td>
<td>37 (32%)</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>183</td>
<td>1-6 yrs</td>
<td>Untreated</td>
<td>...</td>
<td>62 (34%)</td>
<td>121 (66%)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Schermerhorn (1938) [82]</td>
<td>30</td>
<td>&lt;5 yrs</td>
<td>Convalescent</td>
<td>20 mL and 10 mL</td>
<td>Two (spacing 10 days)</td>
<td>22 (73%)</td>
<td>8 (27%)</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>NR</td>
<td>Untreated</td>
<td>...</td>
<td>5 (17%)</td>
<td>24 (82%)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Schermerhorn (1938), Kendrick (1936) [82, 83]</td>
<td>11</td>
<td>&lt;1 yr</td>
<td>Hyperimmune</td>
<td>10 mL</td>
<td>Two (spacing 10 days)</td>
<td>9 (82%)</td>
<td>2 (18%)</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>&lt;1 yr</td>
<td>Untreated</td>
<td>...</td>
<td>1 (20%)</td>
<td>4 (80%)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Cohen and Lapin (1939) [84]</td>
<td>13</td>
<td>Infants</td>
<td>Adult serum</td>
<td>20 or 40 mL</td>
<td>One</td>
<td>8 (62%)</td>
<td>5 (38%)</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Infants</td>
<td>Hyperimmune</td>
<td>10 or 20 mL</td>
<td>One</td>
<td>8 (67%)</td>
<td>4 (33%)</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>Infants</td>
<td>Convalescent</td>
<td>15-40 mL</td>
<td>One</td>
<td>28 (85%)</td>
<td>5 (15%)</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Infants</td>
<td>Untreatedd</td>
<td>...</td>
<td>6 (30%)</td>
<td>14 (70%)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Silvertone and Brown (1942) [85]</td>
<td>25</td>
<td>2 months to 14 yrs</td>
<td>Hyperimmune rabbit</td>
<td>5-10 mL</td>
<td>One</td>
<td>24 (96%)</td>
<td>1 (4%)</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>2 months to 14 yrs</td>
<td>Untreated</td>
<td>...</td>
<td>18 (82%)</td>
<td>7 (18%)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Morris and McDonald (1957) [89]</td>
<td>17</td>
<td>&lt;5 yrs</td>
<td>Hyperimmune IgG fraction</td>
<td>2.5 mL (i.e., 25 mL serum)</td>
<td>One</td>
<td>7 (41%)</td>
<td>10 (59%)</td>
<td>-34%</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>&lt;5 yrs</td>
<td>Untreated</td>
<td>...</td>
<td>9 (56%)</td>
<td>7 (44%)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>&lt;5 yrs</td>
<td>Hyperimmune IgG fraction</td>
<td>2 mL (i.e., 40 mL serum)</td>
<td>One</td>
<td>2 (23%)</td>
<td>6 (75%)</td>
<td>-13%</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>&lt;5 yrs</td>
<td>Untreated</td>
<td>...</td>
<td>3 (33%)</td>
<td>6 (67%)</td>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

NR=not reported, …=not applicable

*a Convalescent, serum from patients recovered from pertussis. Adult, serum from adults without recent pertussis. Hyperimmune, serum from adults or rabbits vaccinated with pertussis vaccine.

b The 2.5 mL and 6 mL IgG fractions represent the equivalent of 25 mL and 90 mL serum, respectively.

c Efficacy was calculated as follows: (number of expected cases-number of observed cases)/number of expected cases. The number of expected cases was based on the number of cases found in the untreated control groups.

d Controls consisted of infants vaccinated prophylactically, which was not effective.
were observed after infusion of the IgG solution, which was well tolerated. In a subsequent phase III clinical trial (25 patients, mean age 9 weeks), no difference was observed in the number or rate of improvement of symptoms (paroxysmal cough, whoop, apnoea, bradycardia, oxygen desaturations) in IgG recipients compared with placebo [94]. However, the trial was prematurely terminated because of expiration of the IgG lots and unavailability of patients.

In summary, studies in animals indicate that immunity against pertussis can be transferred by antibodies. Studies in human beings are confounded by many factors, but when passive vaccination was given before symptoms (i.e., prophylactically), protection was generally observed. By contrast, when passive vaccination was given to infants with symptoms (i.e., therapeutically), little or no effect was found.

**Maternal vaccination against pertussis**

*Animal studies*

A number of studies in animals support the efficacy of maternal vaccination against pertussis. Several studies showed that suckling mice were protected against an aerosol challenge with *B. pertussis* when pregnant mice were immunized with pertussis vaccines or their components [95, 96]. Pertactin, a component of most acellular vaccines, derived from *Bordetella bronchiseptica*, an animal pathogen closely related to *B. pertussis*, was used to vaccinate pregnant sows [97]. After challenge with *B. bronchiseptica*, all 19 (100%) control piglets from unimmunized sows developed pneumonia, coughing, and sneezing, and 14 (74%) of the animals developed severe atrophic rhinitis. In 12 piglets from a sow immunized with pertactin, pneumonia occurred only in 34% of the offspring, coughing was reduced, the duration of coughing bouts was shortened, and severe atrophic rhinitis occurred in only one animal (8%). The difference in the occurrence of atrophic rhinitis and pneumonia in offspring of immunized and non-immunized mothers was significant (P<0.05). More recently, transfer of maternal immunity through colostrum was shown in sows vaccinated with heat-killed *B. pertussis* [98]. Following challenge infection with *B. pertussis*, clinical symptoms, pathological alterations, and bacterial shedding were significantly reduced in piglets that had received passively transferred immunity (P≤0.004). It should be noted that in pigs, maternal antibodies are transferred after birth through colostrum [99].

*Human studies*

Most studies involving vaccination of pregnant women were carried out in the 1930s to 1950s (Table 4). Initially, the aim of the studies was to determine whether protective antibodies were transferred from mother to child. Protective antibodies were assayed in vitro by opsono-
phagocytosis or in vivo by their ability to protect mice from a lethal challenge [54]. Pregnant women selected for these studies had not been vaccinated previously, although most probably had contracted pertussis. In general, high vaccine doses were used, up to six injections each containing $10^{9}$ to $50 \times 10^9$ bacteria (a single dose of a current whole-cell vaccine contains approximately $16 \times 10^9$ bacteria). Injections were given in the arm, subcutaneously, or intramuscularly, in the third trimester.

In all studies, levels of \textit{B. pertussis}-specific antibodies increased in the newborn baby after maternal vaccination compared with newborn babies from untreated mothers. The systemic reactions observed in the mother were few and not severe according to the authors. Local reactions were common, at times very painful, not serious, and sometimes lasted as long as a few days. No effect on the pregnancy or delivery.

In one study, protection in the child was assessed [100]. In this study, the incidence of pertussis in a group of 100 babies of immunized mothers was compared with an equal number of babies of unimmunized mothers. In the first 6 months of infancy, there were six exposures in the unimmunized group, resulting in three cases of pertussis. During the same period there were eight exposures in the immunized group, but no cases of pertussis developed. In the second 6

<table>
<thead>
<tr>
<th>Table 4. Maternal vaccination of pregnant women with pertussis whole-cell vaccines.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pregnant women</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Lichty et al. (1938) [129]</td>
</tr>
<tr>
<td>Mishulow et al. (1942) [54]</td>
</tr>
<tr>
<td>Cohen and Scallon (1943) [130]</td>
</tr>
<tr>
<td>Kendrick et al. (1945) [53]</td>
</tr>
<tr>
<td>Cohen and Scallon (1946) [100]</td>
</tr>
<tr>
<td>Adams et al. (1947) [131]</td>
</tr>
</tbody>
</table>

NR=not reported. Vaccinations in all studies took place in the third trimester of pregnancy.
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.

Side-effects in the mother, as observed in these studies (Table 4), would not be acceptable today. However, whole-cell vaccines have now been replaced by less reactogenic acellular vaccines. Acellular vaccines have been tested in adults in a number of studies (see below) and no serious side-effects were observed.

Safety record of maternal vaccination
Maternal vaccination against tetanus has been used worldwide since the 1970s [101] and no evidence has been presented of negative effects on pregnancy or the neonate. Vaccination of pregnant women has been practiced extensively in the USA since 1957 [29, 102]. The greatest use occurred before 1966, when vaccination with both influenza and poliovirus vaccines was recommended during pregnancy. The safety of this procedure was documented by the large Collaborative Perinatal Project in which over 50,000 pregnant women were enrolled between 1959 and 1965 [103]. The offspring was followed until 7 years of age for malformations, hearing impairment, and learning disabilities. The most common vaccine used was inactivated poliovirus vaccine, which 18,342 women received, whereas 3,056 received live attenuated oral poliovirus vaccine at some time during pregnancy. Influenza vaccine was given to 2,291 women. Based on extrapolation from the vaccination rates of women in this study, it is estimated that 2 million doses of vaccines were given to pregnant women each year between 1959 and 1965. Vaccination of women during pregnancy was not associated with adverse outcomes or an increased risk for any disability in the infants in this study. However, these studies might not have been large enough to detect congenital abnormality or foetal loss. Inactivated influenza vaccine is currently recommended by the US Centres 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 [104].

Controlled trials done in recent years with bacterial (Hib, group B streptococci, *S. pneumoniae*) and viral vaccines (influenza, respiratory syncytial virus, rubella virus, poliovirus) have provided no evidence of adverse outcomes for mother or child [28, 105-109]. Furthermore, no evidence was found that maternal vaccination affected active vaccination of infants. Infants of women who received vaccines had, in general, developed responses to active vaccination that were similar to those of infants whose mothers were not vaccinated [29].
Safety of acellular vaccines in adults
Maternal vaccinations have been carried out with whole-cell vaccines, which are known to be relatively reactogenic. In many countries, whole-cell vaccines have been replaced by acellular vaccines, which show fewer side-effects compared with whole-cell vaccines [110]. To reduce circulation of *B. pertussis* in human populations, universal adolescent and adult vaccination is considered, or already implemented, in a number of countries [7, 111].

A large proportion of adults may have high pertussis antibody levels because of recent infection with *B. pertussis* [112] and there is some concern that using infant doses for adult vaccination could result in side-effects because of high levels of pre-existing antibodies. Therefore, adult formulations have been developed that have a lower content of antigens compared with infant pertussis vaccines. Safety trials have been done with vaccines with adult formulations. In most studies a single booster was given. However, in one trial a second dose of acellular vaccine was given [113]. The second dose was not associated with increased adverse events in adults but elicited increased antibody titres over that achieved by a single dose against pertussis toxin only. In another study [114], it was noted that vigorous serum antibody responses to several pertussis antigens were associated with an increased risk of developing late-onset reactions (pain, tenderness, induration or erythema at the site of injection), as has been observed after vaccination with diphtheria toxoid [115]. If high levels of pre-existing immunity are a risk factor for more serious side-effects, it may be advisable to limit vaccination of pregnant mothers to those with low anti-pertussis titres.

The studies with acellular vaccines in adolescents and adults showed that side-effects were generally mild and not substantially different from control vaccines without the pertussis component (e.g., vaccines containing diphtheria and tetanus toxoids) [116]. Furthermore, the adult formulations were immunogenic and, importantly, pre-existing antibody did not have an inhibitory effect on the response to vaccination [116, 117]. It seems likely that acellular vaccines will have a much improved safety profile in pregnant women compared with the whole-cell vaccines that have been tested. In fact, according to the recommendations of the US Advisory Committee on Immunization Practices (ACIP), pregnancy is not a contraindication for vaccination with adult formulations of a combined tetanus, diphtheria, acellular pertussis vaccine [118].

Discussion
Maternal vaccination may substantially reduce pertussis morbidity and mortality in infants too young to be fully vaccinated. A major obstacle for its introduction is concern about side-effects in mother and child. However, maternal vaccination has been shown to be effective and
safe for tetanus toxoid over long periods of time. Furthermore, maternal vaccination studies with whole-cell vaccines done in the past have not shown serious side-effects in mother or child. In one study, maternal vaccination was shown to protect newborn babies. Because maternal vaccination 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, albeit in varying degrees. An important gap in our knowledge is the level of maternal antibodies required for protection of the child. However, levels of antibody against pertussis toxin, pertactin, and fimbriae (or agglutinogens) have been established that are associated with protection, and adult formulations of acellular vaccines induce high levels of antibodies against these antigens. Importantly, adult formulations of acellular vaccines have been found to be safe and are recommended for adolescent and adult vaccination in a number of countries. Additionally, pregnancy is not deemed a contraindication for vaccination with adult formulations of acellular vaccines according to the recommendations of the ACIP. However, there is some evidence that high levels of pre-existing immunity in adults are a risk factor for side-effects of vaccination and this issue needs to be investigated further. Another issue that should be addressed is whether maternal immunization will affect the infant’s immune response to primary vaccination. Ultimately, safety and efficacy of maternal vaccination will have to be assessed in clinical trials. An advantage of maternal vaccination is the accessibility of the targeted group, since both (pregnant) mothers and infants frequently visit health-care centres. Finally, maternal vaccination could also have beneficial effects for childhood diseases other than pertussis, especially in the low-income countries where it could help to prevent the 2-3 million neonatal and early infant deaths every year [119].

**Acknowledgements**

We are grateful to Tjeerd Kimman, Joop Schellekens, and Florens Versteegh for critically reviewing this manuscript and discussions.
References

156


