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

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Impact of acellular pertussis preschool booster vaccination on disease burden of pertussis in the Netherlands

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Abstract

Background: An acellular preschool booster vaccination against pertussis has been included in the National Immunization Programme in the Netherlands, since November 2001. We studied the impact of this preschool booster on the epidemiology of pertussis.

Methods: We analysed and compared pertussis cases registered in the national notification system, hospital registry, and death registry between the periods 1998-2001 (without preschool booster) and 2002-2005 (with preschool booster).

Results: In 2002-2005, the incidence of hospitalisations and notifications in 1-4-year-olds were 48% and 44%, lower respectively, than in 1998-2001. Similarly, in 5-9-year-olds the incidence of hospitalisations and notifications had decreased 32% and 15%, respectively.

In 2005, vaccine effectiveness for the preschool booster among children born between January 1, 1998 and January 1, 2001 – all of whom had been eligible for the booster – was estimated at 79% (95%CI: 71-85). In infants aged 0-6 months, the incidence of hospitalisations per 100,000 population decreased 40%, from 222.5 to 133.6. In contrast, among cohorts aged 10-19, 20-59, and ≥ 60 years, the incidence of notifications increased 60%, 44%, and 68%, respectively.

Conclusions: The preschool booster strongly decreased the disease burden in the targeted cohorts. Importantly, the incidence in infants 0-6 months also showed a decline after introduction of the preschool booster, suggesting reduced transmission from siblings to young infants. Meanwhile, the number of pertussis cases in adolescents and adults increased. With prevention of severe pertussis among infants as focus, this effect should not be ignored in the discussion on future vaccination strategies for pertussis.
Introduction
Vaccination against pertussis has resulted in an enormous decrease of the disease incidence and above all of disease severity, especially in developed countries [1]. Despite high vaccine coverage (ca. 96%), surveillance sources revealed an outbreak of pertussis among mostly vaccinated children in the Netherlands in 1996-1997 [2]. Changes in vaccination coverage, in diagnostic procedures, in notification practice, and interference with other vaccinations could not explain the epidemic. The sudden increase among vaccinated children in combination with changes in the *Bordetella pertussis* population and the low immunogenicity profile of the Dutch whole-cell vaccine used at that time supported the hypothesis that, because of antigenic changes, *B. pertussis* was less affected by vaccine-derived immunity [2, 3]. A number of other countries also experienced a resurgence of pertussis in the last decade, especially among adolescents and adults [4-6]. Although these increases might be partly the result of improved recognition and surveillance, the trend is worrisome. Indeed, many recent studies suggest that the increased circulation of *B. pertussis* among adults and adolescents has led to increased morbidity and mortality in infants too young to be (fully) vaccinated [7, 8]. Unvaccinated infants are at greatest risk for severe complications or death as a result of pertussis. Because in most countries the first pertussis vaccinations are given after the age of 2 months, protection in this period relies on (incomplete) herd-immunity [9]. Different strategies have been considered to complement or improve current vaccination schedules resulting in better protection of these young infants: maternal immunization [10], universal adult or adolescent immunization, selective immunization of close family members of newborns, selective immunization of child-care workers, reinforcement of the current strategy by enhancing vaccine coverage, and a preschool booster at 4-6 years of age [11].

Because of the high incidence of pertussis among school children in the Netherlands [2] the latter strategy, an acellular booster dose in the year a child turns 4 years of age, has been included in the National Immunization Programme (NIP) since the end of 2001. Other countries that have introduced a preschool booster, report a decreasing incidence in the age groups targeted for the booster vaccination [12, 13]. However, as yet little is known about the duration of protection from the preschool booster against disease and its effectiveness in reducing overall pertussis morbidity through herd-immunity.

To assess the impact of the introduction of a preschool booster on the incidence of pertussis, we studied age-specific trends in pertussis epidemiology in the Netherlands in the period 1998-2001 (when no preschool booster was given) and 2002-2005 (when an acellular pertussis preschool booster vaccination was given). The current study extends a previous report on the routine surveillance data from pertussis in the Netherlands covering the period from 1976-1997 [2].
Methods

Case reporting

Since 1976, notification of pertussis to the Health Care Inspectorate has been obligatory by law in the Netherlands. Disease notification data are presented by the date of onset for the period January 1, 1998 to December 31, 2005.

Since 1988, the case definition for notification includes a clinical picture compatible with pertussis (i.e., serious cough with a duration of more than 2 weeks, coughing attacks, or cough followed by vomiting) in combination with: isolation of \textit{B. pertussis} or \textit{B. parapertussis}, detection of \textit{B. pertussis} or \textit{B. parapertussis} DNA by polymerase chain reaction (PCR), or a significant rise in IgG antibodies against pertussis toxin (Ptx) or IgA antibodies against whole cell sonicate of \textit{B. pertussis} in paired serum samples, or a single serum sample with IgA/IgG- Ptx titres above a defined age-specific cut-off value [14], or contact in the last 3 weeks with a laboratory confirmed patient with \textit{B. pertussis} or \textit{B. parapertussis} infection. PCR as a method of confirmation for notification has been accepted since 1997. This case definition has not changed during the period of study. Since 1998, the percentage of infants $\leq$1 year in whom pertussis was confirmed by PCR or culture varied between 30% and 45%. In children $>$1 year and adults, about 5% of the pertussis cases were confirmed by PCR or culture. In the remaining patients pertussis was serologically confirmed. These percentages have not changed during the period of study. Fewer than 5% of PCR or culture confirmed cases are \textit{B. parapertussis} positive in the Netherlands [15]. More detailed information regarding the notification system for pertussis can be obtained from de Greeff et al. [16].

Hospital admissions and deaths

Hospital episodes of pertussis from January 1998 through December 2005 were extracted from the National Medical Register. Diagnoses were recorded using the 9th International Classification of Diseases based on clinical diagnoses. Cases with code 0330 (Whooping cough caused by \textit{B. pertussis}), 0331 (Whooping cough caused by \textit{B. parapertussis}), 0338 (Whooping cough caused by other specified organism), or 0339 (Whooping cough caused by unspecified organism) as main discharge diagnosis were included. The annual number of deaths in the period of study caused by pertussis (ICD-10 code A370, A371, A378, and A379) was obtained from Central Statistics in the Netherlands.

Vaccine schedule and vaccines used

In the Netherlands, nationwide pertussis vaccination has been implemented in the NIP since 1957. Until 1999, vaccination with a combined diphtheria, tetanus, pertussis and inactivated polio vaccine (DTP-IPV) was given at 3, 4, 5, and 11 months of age. Since 1999, this schedule
has been accelerated and nowadays children are vaccinated at 2, 3, 4, and 11 months. Until 2004, a nationally manufactured whole-cell vaccine was used as pertussis component of DTP-IPV for the primary series. In 1997, small changes in the production process of the vaccine in the Netherlands were implemented, resulting in a higher protection as measured in the release test in mice, and in an increased consistency of the production process. The whole cell vaccine was replaced by a 3-component vaccine (Infanrix-IPV-HIB, from GSK) in 2005, followed by a 5-component acellular vaccine (Pediacil; Sanofi, Val de Reuil, France) in 2006.

For the preschool booster vaccination introduced in 2001, a 3-component acellular vaccine was used (by GSK), which was given concomitantly, but as a separate injection, with DT-IPV. During the period under study in this article, children who were eligible for the preschool booster could according to the NIP only have been primed with a whole-cell vaccine.

**Statistical analyses**

The number of notifications, hospital admissions, and deaths as a result of pertussis per year, per month, and per age group were extracted from the different registrations. To calculate annual incidence rates/100,000, the total number of cases for a year was divided by the total population on the first of January of the relevant year. To study the effect of the preschool booster, average incidence rates in the 4 years before (1998-2001) and 4 years after (2002-2005) introduction of the preschool booster were compared. In this way, the effect of year to year fluctuations was minimized.

Age-specific average incidence rates in both periods were compared as incidence rate ratios (relative risks or RR) with 95% confidence intervals (95%CI). Vaccine-effectiveness (VE) for vaccination in age groups targeted for the fifth dose, were estimated from notifications according to the screenings method, whereby estimates were derived using the equation:

$$VE(\%) = 1 - \frac{PCV}{(1-PCV) \times (1-PPV) / PPV},$$  

where PCV is the proportion of notified cases that has been vaccinated and PPV the proportion of the population that has been vaccinated. The PPV was assumed to be 93% for the preschool booster [18]. Incompletely vaccinated cases were excluded from the estimation, 95% confidence intervals were calculated as described in Hightower et al. [19]. Calculations were performed using SAS version 9.1, Excel, and Episheet [20].
Results

Annual incidence rate

In the period 1998-2005, the annual incidence rate of pertussis notifications varied between 16.0 in 1998 and 59.8 in 2004 and for the hospitalisations between 0.9 in 2003 and 3.0 in 1999 (Figure 1). Every 2-3 years, an increase in both incidence rates took place, with peaks reported in 1999 (notifications 44.3, hospitalisations 3.0), 2001 (notifications 50.2, hospitalisations 2.3), and 2004 (notifications 59.8, hospitalisations 1.8) (Figure 1). Notifications for pertussis showed an increasing trend, whereas for the hospitalisations a decreasing trend in pertussis incidence was observed.

From 1998 until 2005, 5 deaths as a result of pertussis were reported: 1 in 1998, 3 in 1999, and 1 in 2004, all were children <3 months of age.

The overall incidence rate in the period when no preschool booster was given (1998-2001) compared with the period when the preschool booster was included in the NIP (2002-2005), was almost similar for notifications (34.3 versus 35.3, respectively), whereas for hospitalisations the incidence rate decreased (2.1 versus 1.4, respectively).

Age-specific incidence rates

In agreement with the overall trends, peaks in notifications occurred for all age groups in 1999, 2001, and 2004 (Figure 2). The peaks of notified cases among cohorts aged 0-year and 5-9 years remained almost equally high. In contrast, the height of the peaks among 1-4-year-olds decreased and among adolescents (10-19 years) and adults (20-59 years and ≥60 years) a significant increase was seen (Figure 2).

Figure 1. Yearly incidence of notified pertussis cases (bars) and hospitalised pertussis cases (line) in 1998-2005.
Furthermore, for hospitalisations in infants and children <10 years of age, the height of the peak in 2004 was lower than in 2001, whereas among the older children and adults the peak in 2004 was higher than in 2001 (Figure 2).

In Table 1, age-specific incidence rates for hospitalisations and notifications per 100,000 population in the period without (1998-2001) and with (2002-2005) a preschool booster are presented. For comparison of both periods, incidence rate ratios (relative risks) are presented. Among 1-4 and 5-9 years old cohorts – both of which contain individuals eligible for the booster – the RR for hospitalisations in the period when a preschool booster was given

Figure 2. Annual incidence/100,000 of hospitalisations on left axis (line) and notified pertussis cases on right axis (dotted line) by age category in 1998-2005.
were 0.52 (95%CI: 0.41-0.66) and 0.68 (95%CI: 0.49-0.94), respectively (Table 1). This corresponds with a decrease of hospitalisations among 1-4-year and 5-9-year-olds of 48% and 32%, respectively, in the booster period. Similarly, the incidence rate for notifications among 1-4 and 5-9-year-old cohorts decreased with, respectively, 44% and 15% between both periods (Table 1).

The relative risk for hospitalisations and notifications in 0-5-months-old infants amounted to 0.60 (95%CI: 0.54-0.67) and 0.80 (95%CI: 0.71-0.89), respectively. Thus, the incidence rates of hospitalisations and notifications among infants <6 months of age were 40% and 20%, respectively, lower in the period when a preschool booster was included (Table 1). This decrease in incidence rates was seen for both unvaccinated as well as partly vaccinated infants <6 months of age. Compared with the period before introduction of the booster, the incidence rates of hospitalisations for the 0-1 month, 2-3 month, and 4-5 month age group decreased with 44%, 35%, and 42%, respectively.

To rule out the effect of the replacement of the Dutch whole cell vaccine by an acellular vaccine for the primary series in 2005 in our calculations, we also compared incidence rates in the period 1998-2001 with 2002-2004. This comparison still revealed a 37% reduction (RR=0.63, 95%CI: 0.56-0.70) in hospitalisations and 19% reduction (RR=0.81, 95%CI: 0.71-0.91) in notifications in infants <6 months of age.

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<tr>
<td>0-5 months</td>
<td>222.5</td>
<td>166.1</td>
<td>133.6</td>
<td>132.3</td>
<td>0.60 (0.54-0.67)</td>
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<td>6-11 months</td>
<td>26.5</td>
<td>82.4</td>
<td>30.2</td>
<td>84.9</td>
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<tr>
<td>1-4 years</td>
<td>6.5</td>
<td>153.8</td>
<td>3.4</td>
<td>86.5</td>
<td>0.52 (0.41-0.66)</td>
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<td>5-9 years</td>
<td>2.3</td>
<td>199.0</td>
<td>1.6</td>
<td>168.6</td>
<td>0.88 (0.49-1.66)</td>
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<td>9-10 years</td>
<td>0.3</td>
<td>42.6</td>
<td>0.3</td>
<td>68.2</td>
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<td>10-19 years</td>
<td>0.1</td>
<td>10.9</td>
<td>0.1</td>
<td>15.7</td>
<td>1.89 (0.59-2.03)</td>
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<td>20-59 years</td>
<td>0.1</td>
<td>7.0</td>
<td>0.1</td>
<td>11.7</td>
<td>1.37 (0.63-2.96)</td>
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<tr>
<td>≥ 60 years</td>
<td>0.1</td>
<td>7.0</td>
<td>0.1</td>
<td>11.7</td>
<td>1.37 (0.63-2.96)</td>
</tr>
<tr>
<td>total</td>
<td>2.1</td>
<td>34.3</td>
<td>1.4</td>
<td>35.3</td>
<td>0.65 (0.59-0.70)</td>
</tr>
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Table 1. Age-specific incidence rates per 100,000 population for pertussis hospitalisations and notifications in 1998-2001 and 2002-2005, and relative risk (95%CI) for comparison of the incidence rates between both periods.
In contrast, among the 10-19, 20-59, and over 60-year-olds, the incidence rates of both hospitalisations and notifications were substantially higher in the periods 2002-2005 than in 1998-2001. Between both periods the incidence of hospitalisations among 10-19, 20-59, and over 60-year-olds had increased 4%, 9%, and 37%, respectively (Table 1). During the same periods, the incidence of notifications in these age groups had increased 60%, 44%, and 68%, respectively.

Vaccine-effectiveness
VE for the preschool booster among children born between January 1, 1998 and January 1, 2001 — all of whom had been eligible for the booster — was estimated in 2005 at 79% (95%CI: 71-85). For the first (year of birth 1998), second (year of birth 1999) and third (year of birth 2000) cohort who became eligible for the booster, the VE in 2005 amounted to 73% (95%CI: 40-88), 74% (95%CI: 54-86) and 84% (95%CI: 75-90), respectively.

Discussion
Despite a high vaccination coverage in infancy (>96%), pertussis is still endemic in the Netherlands. After the sudden upsurge in 1996-1997, the incidence of pertussis has remained significantly higher than in the period before 1996 [2], with peak rates observed every 2-3 years [21]. The introduction of the preschool booster vaccination for 4-year-olds with an acellular vaccine in 2001 caused a significant decrease in the incidence of pertussis among the targeted population. No evidence was found for waning immunity 4 years after the preschool booster as the estimated VE remained high, 73%-84%, in the vaccinated cohort. The observed decline in the incidence among young infants suggests that the preschool booster has indirectly protected these susceptible infants. By contrast, in the same period the incidence among adolescents and adults increased.

Before introduction of the preschool booster in 2001, peak incidences for notified cases occurred among unvaccinated or incompletely vaccinated infants <6 months of age and among schoolchildren aged 4-5 years [2]. Apparently, as a result of waning vaccine-derived immunity a substantial number of vaccinated children were again susceptible to pertussis before school entry. Because acellular vaccines were expected to cause fewer side effects and to be more efficacious, the Dutch whole-cell vaccine was replaced by an acellular vaccine in 2005. The expectation is that this will delay the waning of vaccine-derived immunity. Nevertheless, Swedish studies have shown that immunity induced by acellular vaccines in infancy is still limited to about 5-7 years [22, 23].
One important finding of our study was the beneficial effect of the preschool booster on the incidence of pertussis in infants. In Australia, a fifth dose at 4 years of age has been recommended since 1994. Although high coverage was achieved, a downward trend was seen only in the notification rate of the targeted age group [12]. In fact, the United States reported an increase in morbidity [7] and mortality [8] among infants, despite the use of an acellular preschool booster since 1997. Similarly in New Zealand, an increase in infant pertussis was seen despite 4 doses in infancy and 1 at preschool age [24]. Based on mathematical modelling, Hviid et al. [25] estimated that a preschool booster could prevent 18% of hospitalisations in infancy, but our study suggests that a much higher proportion of severe disease is prevented by the preschool booster. Indeed, the incidence of severe disease, resulting in hospitalisation, among infants less than 6 months of age decreased 40% between 1998-2001 and 2002-2005. Part of the reduction of pertussis among infants might be attributable to the replacement of the whole cell vaccine with a more effective acellular vaccine in 2005. However, analysis of a period when only the whole cell vaccine was used still revealed 37% reduction in hospitalisations in infants less than 6 months of age. This finding suggests that in the Netherlands transmission from siblings to susceptible infants may have been reduced as a result of the preschool booster. Such a herd-immunity effect was not observed for infants aged 6-11 months. Although this may be because of different contact patterns of this age group, the interpretation is also difficult because of the small numbers of infants involved. The accelerated vaccination schedule in place since 1999 could also have contributed to the decreased incidence in infants less than six months. Especially the ≥2-month-olds would have benefited from this. However, as similar decreases in hospitalisations are seen in the <2-month-olds (i.e., the unvaccinated age group), the herd-immunity effect caused by the preschool booster seems to be the most important factor. It may be anticipated that the incidence in the 6-11 months age group will decline more after the introduction of the acellular vaccine in 2005 [26].

It seemed that siblings used to be important sources of infection in infants in the Netherlands. This does not correspond with findings from other studies which found that in regions with a low vaccination coverage children were the main source of infection in infants, whereas in high coverage regions – as in the Netherlands – adults played a relatively larger role [27, 28]. Perhaps, lower immunogenicity of the Dutch whole-cell vaccine since the 1990s combined with changes in the pathogen in that period have reduced the functional vaccine coverage. The reduction in infant morbidity might have been more pronounced if morbidity in adults had not increased [29, 30]. An increase in the number of adolescents and adults with pertussis has also been seen in other countries in Europe [4], the United States [5], Canada [6], and Australia [12]. Estimations of infection frequencies with \( B. \) \( pertussis \), irrespective of clinical course, have shown that infections in adolescents and adults are substantially higher than reported
in notification systems [31]. This increased incidence in countries with continuously high vaccination coverage is often attributed to better case reporting as a result of more sensitive diagnostic methods or increased awareness of pertussis in these groups. It is important to acknowledge these artefacts in our results. Although PCR as method of diagnosis has partly replaced culture, still only approximately 5% of notifications are confirmed by PCR in the Netherlands, the rest by serology, and these proportions have not changed recently. The narrowed gap between the incidence based on notifications and hospitalisations in infants in the more recent period suggests that a higher proportion of hospitalised cases is being notified. From general practitioner sentinel stations we know that increased alertness has led to a larger proportion of patients being identified (data not shown), both adults and children. Increased alertness may have partly affected increasing trends in adolescents and adults. However, the observation that epidemiological trends in hospitalisations equal the trends in notifications makes it plausible that changes in the number of notified cases are true changes even though the extent may have been affected by more reliable notification practice.

The increased incidence among adolescents and adults might be partly attributed to waning of vaccine-induced immunity [9, 32, 33]. In addition pathogen adaptation may play a role, as antigenic divergence between vaccine strains and circulating strains has been observed [3, 34]. Several independent studies have shown that strain variation affects vaccine efficacy in the mouse model [35, 36]. Recently vaccinated children are well protected, but this mismatch may shorten the period in which reinfection can occur after vaccination.

Modelling studies have shown that booster vaccinations for adults and adolescents are promising approaches to reduce overall morbidity and mortality of pertussis [37]. The true impact of these strategies on disease burden in infancy depends on accessibility of the target population and transmission patterns between age groups, which apparently differ among countries. Because vaccines do not offer lifelong protection as a result of waning immunity, transmission from adolescents or adults to infants takes place unless boosting is repeated [38]. It might be more effective in the long term to protect young infants earlier in life, by vaccination at birth or through maternal antibodies induced by vaccination of the mother during pregnancy [10]. With prevention of pertussis among infants as focus, the relative and country-specific importance of the sources of infection for these infants (e.g., adults, siblings) needs to be determined. These data can be used to assess, by dynamic modelling, the most effective vaccination strategy to prevent pertussis in infants.
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