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

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General introduction
History of pertussis epidemiology and vaccination

Pertussis is a highly contagious infectious disease of the respiratory tract. Typical pertussis illness usually starts after an incubation period of 7-20 days. The initial (catarrhal) phase is indistinguishable from common upper respiratory infections with two weeks of nasal congestion, rhinorrhea, and sneezing. In the following (paroxysmal) phase, with cough mostly lasting for more than 28 days, typical pertussis symptoms occur such as paroxysmal coughing, post-tussive vomiting and/or inspiratory whooping. In unvaccinated infants the infection is most severe and is often accompanied by cyanosis, apnoea, and seizures. In some cases severe complications may ensue such as pneumonia, encephalopathy or even death [1]. Although typical pertussis may occur, most older children and adults with pertussis report relatively mild disease with long term coughing and cold like symptoms [2, 3].

The first written description of a pertussis epidemic occurred in Paris and dates from 1578 [4]. In the subsequent centuries more epidemics in Europe were described, suggesting the disease expanded [5]. Anecdotic case reports and names of diseases that resemble the currently known names for whooping cough (kinkhoest, keuchhusten, coqueluche, pertussis, tussis quinta, tosse canina, tosse asinina) have been found in old dictionaries, articles, and medical books between the 16th and the 20th century [6-8]. At the time it was not clear what caused the disease and by some its contagiousness was ascribed to the involuntary imitation also observed with yawning: if one persons coughs, this may cause another person to “sympathetically” cough [9]. Later, in the 20th century it became clear that pertussis was caused by an infectious agent. The causative organism Bordetella pertussis was first isolated in 1906 by Bordet and Gengou and initially named Haemophilus pertussis [10]. Later, two other Bordetella species isolated from patients suspected of pertussis were identified, designated Bordetella parapertussis and Bordetella bronchiseptica [11, 12]. B. bronchiseptica is rarely isolated from pertussis patients and most of these infections are of zoonotic origin. However, like B. pertussis, B. parapertussis is a human pathogen. It generally causes a milder form of pertussis and in the Netherlands it is isolated from circa 5% of the pertussis patients.

Routinely collected data on disease frequency and distribution of pertussis are available since the 20th century. Before the introduction of vaccination, pertussis was a major cause of infant death worldwide. In 1934-1943, on average 4,000 deaths due to pertussis were reported each year in the US (3.2/100,000) and 350 in the Netherlands (3.5/100,000) [13, 14]. In both countries more than 95% of deaths occurred in children below 5 years of age. Although pertussis was mainly seen as a disease in childhood, clinical case data from the prevaccination era indicate that reinfections in adults were common [6]. In the 1940s, effective whole-cell vaccines against B. pertussis were developed, which were based on killed and detoxified bacteria. In the Netherlands, a single pertussis vaccine was produced by the National Institute
for Public Health (RIV) in 1949, and from 1952 a combination vaccine against diphtheria, pertussis and tetanus became available (DTP) [13, 15]. In the beginning of the 1950s, the annual number of reported deaths due to pertussis decreased to thirty and cases of typical pertussis in children diminished, though atypical pertussis in immunized infants was still reported [16]. In 1953, DTP vaccination was free available for mass vaccination by general practitioners, child-care centres and school doctors, and the uptake of the vaccine increased in the beginning of the 1950s [13]. In 1955, an injectable polio vaccine (IPV) was registered in the US. After the epidemic of poliomyelitis in 1956 the government requested - on advice of the Health Council - the RIV to produce IPV itself and the Health Care Inspectorate was solicited to organize vaccination campaigns intending to vaccinate all children in the Netherlands. This mass vaccination against polio was the start of the National Immunization Programme (NIP). Initially, vaccination was provided against diphtheria, whooping cough, tetanus and polio (DTP-IPV). In the 1970-1980s, the program was extended to also provide protection against measles, mumps, and German measles (rubella) (MMR). Since the 1990s, vaccinations against hepatitis B, Haemophilus influenzae type b (Hib), meningococcus C and pneumococci have been included.

**Figure 1.** Annual number of deaths due to pertussis in the Netherlands 1905-1977 (upper figure), 1978-2008 (lower figure).
Already before introduction of vaccination the mortality of pertussis decreased (Figure 1), presumably due to the higher standard of living, smaller families, improved nutritional status, and the effective treatment of pulmonary complications with antibiotics [13, 17]. In the first years after introduction of routine vaccination, not only the mortality of pertussis decreased but also the case-lethality (i.e., mortality per pertussis case) [13]. In the 1960s and 1970s, the number of deaths decreased to less than 5 per year [18].

As pertussis became rarer in many countries, the need for pertussis vaccination was questioned and the attention shifted from the disease to the adverse events that sometimes follow vaccination. In several countries, suspicions arose that whole-cell pertussis vaccines could very rarely cause serious neurological complications, such as encephalopathy or even death. In Japan, whole-cell pertussis vaccination was eliminated in the end of the 1970s after two infants died within 24 hours of receiving DTP vaccine. In Sweden, after 20 years of vaccination, the efficacy and safety of the vaccine were questioned because pertussis still occurred in vaccinated children and some neurological events after vaccination were blamed on the vaccine. Subsequently, Sweden banned the use of whole-cell vaccination in 1979. In the UK vaccine uptake dropped from 80% in the early 1970s to 30% in 1975 after the public confidence in pertussis vaccination collapsed following reports linking the vaccine with brain damage [19]. Although investigations could not find a causal link between whole-cell pertussis vaccines and severe events, concerns about safety led to the development of acellular pertussis vaccines in the 1970s [20, 21]. Acellular vaccines consist of up to five specific purified *B. pertussis* antigens (pertussis toxin, filamentous haemagglutinin, pertactin, and two fimbrial antigens) and were tested to be non-inferior to whole-cell vaccines but caused fewer side-effects [22].

In the Netherlands in 1976-1984, because of professional and public anxiety concerning the side effects of whole-cell vaccines, the potency of the Dutch vaccine was reduced [23]. Although the vaccine coverage remained high, the number of patients with pertussis increased in the beginning of the 1980s [24]. At that time, it was not clear whether the increased incidence was related to the lower potency of the vaccine or to increased awareness, the establishment of a mandatory notification system or the development of serologic methods for diagnosis. However, later studies showed that the reduction in vaccine potency was followed by significant changes in the *B. pertussis* population, suggesting changes in host immunity. Thus, the increase in notifications may at least in part reflect a true epidemic [25]. In 1989-1994, the disease was endemic in childhood with 4-yearly peaks and most severe disease in infants [26].
Recent developments in the epidemiology of pertussis

Despite more than half a century of vaccination, pertussis is - from all vaccine preventable diseases for which a vaccine was licensed before 1980 - the disease with relatively the lowest reduction in number of cases [14]. Globally, approximately 300,000 children still die from pertussis each year especially in developing countries [27, 28].

Pertussis vaccination helps to prevent disease, but infection may still occur. In addition, neither vaccination nor natural infection provides lifelong protection. Due to waning of vaccine-induced and natural immunity, reinfection may occur and circulation of the bacterium can continue. The severity of the symptoms is affected by the patients’ age, clinical condition, and previous exposure to the organism (either by vaccination or prior infection). Consequently, pertussis infection nowadays has a wide spectrum of clinical manifestations varying from very severe in unvaccinated infants to mild or even asymptomatic in vaccinated children and adults.

In 1996-1997, an outbreak of pertussis occurred in all age groups in the Netherlands especially among vaccinated patients [29]. Changes in vaccination coverage, in diagnostic procedures, in notification practice, and interference from other vaccinations, could not explain the epidemic [29, 30]. The sudden increase among vaccinated children in combination with observed changes in the \textit{B. pertussis} population supported the hypothesis that, due to antigenic changes, circulating strains of \textit{B. pertussis} had become less sensitive to vaccine-induced immunity [30-32]. The effect of antigenic changes may have been aggravated by the low immunogenicity profile of the Dutch whole-cell vaccine used at that time. Since the sudden upsurge in 1996-1997, the incidence of reported pertussis cases has remained high with peaks every 2-3 years (Figure 2).

A number of other countries also experienced a resurgence of pertussis in the last decade, especially among adolescents and adults [2, 3, 33-35].

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{pertussis-outbreak.png}
\caption{Monthly number of cases notified for pertussis in the Netherlands 1989-2009.}
\end{figure}
Due to the re-emergence of pertussis the vaccination strategy for pertussis has changed in the Netherlands. Until 1999, children were vaccinated at the age of 3, 4, 5, and 11 months, and after 1999 this schedule was enhanced by decreasing the age for the first vaccinations to 2, 3, 4, and 11 months [36, 37]. Because of the high incidence in 5-9-year-olds, in November 2001 an acellular booster vaccination for four-year-olds was introduced in the NIP [38]. Because of concerns on side-effects and effectivity, the Dutch whole-cell vaccine was replaced by an acellular vaccine in 2005 [39]. Recent changes regarding pertussis vaccination in the NIP are summarized in Table 1.

Since healthy children are exposed to vaccinations recommended by the government, it is a governmental responsibility to monitor the effectiveness, safety, and reliability of (changes in) the nationwide vaccination programme. The evaluation of the NIP consists of five pillars involving surveillance of: disease incidence, immune status, the pathogen population, safety, and vaccination coverage [40]. Whereby surveillance is defined as: the ongoing systematic collection and analysis of data and the provision of information which leads to action being taken to prevent and control a disease [41].

Table 1. Recent changes regarding pertussis vaccination in the Netherlands.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
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<tbody>
<tr>
<td>1997 (November)</td>
<td>Introduction of a ‘stronger’ whole-cell vaccine into the National Immunization Programme, i.e. the criteria for release of the vaccine were enhanced, in that lots were required to contain at least seven International Units (IU) instead of 4 IU.</td>
</tr>
<tr>
<td>1999 (January)</td>
<td>Acceleration of vaccine schedule from 3, 4, 5, 11 months after birth to 2, 3, 4, 11 months after birth.</td>
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<tr>
<td>2001 (October)</td>
<td>Introduction of acellular booster vaccination at 4 years of age for children born from 1\textsuperscript{st} January 1998 onwards.</td>
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<tr>
<td>2003 (March)</td>
<td>Introduction of combined vaccine DTwP-IPV-Hib at 2, 3, 4, and 11 months, for birth cohorts from 1\textsuperscript{st} April 2002 onwards.</td>
</tr>
<tr>
<td>2005 (January)</td>
<td>Replacement of DTwP-IPV-Hib (NVI) with DTaP-IPV-Hib (Infanrix IPV-Hib (GSK)) at 2, 3, 4, and 11 months, for birth cohorts from 1\textsuperscript{st} February 2004 onwards.</td>
</tr>
<tr>
<td>2006 (January)</td>
<td>Replacement of Infanrix IPV-Hib (GSK) by Pediacel (SP MSD) at 2, 3, 4, and 11 months, for birth cohorts from 1\textsuperscript{st} February 2005 onwards.</td>
</tr>
<tr>
<td>2006 (July)</td>
<td>Introduction of combined DTaP-IPV vaccine (Triaxis Polio, SP) for children at 4 years of age born from July/August 2002 onwards.</td>
</tr>
<tr>
<td>2008 (January)</td>
<td>Replacement of Pediacel (SP MSD) by Infanrix IPV-Hib (GSK) at 2, 3, 4, and 11 months. Infanrix IPV (GSK) also available for 4-year-olds.</td>
</tr>
</tbody>
</table>
Outline of the thesis
The main objectives of the studies described in this thesis are to explain trends in the epidemiology of pertussis in the Netherlands in the past decade, and to guide policy and development of control strategies for pertussis in the Netherlands. The studies in this thesis are predominantly based on disease surveillance, a method used to give a description of the frequency and distribution of the disease. Disease surveillance for pertussis in the Netherlands relies on mandatory notifications, laboratory reports, GP sentinel registrations, death registrations, and hospital discharge diagnoses from the National Medical Register. Besides studying trends in the prevalence of pertussis, based on the reported number of pertussis cases in infants, a household study was conducted to investigate transmission routes for pertussis. However, since pertussis infections can be mild or asymptomatic and consultation of a general practitioner is often not required, these clinical surveillance sources underestimate the true number of pertussis infections. To provide insight into the prevalence of clinical disease as well as subclinical infections we used immunosurveillance, which is the assessment of specific antibodies in serum to indicate exposure to a pathogen by vaccination or natural infection.

Surveillance of the vaccination coverage was used to estimate vaccine effectiveness. Nowadays, the coverage for pertussis vaccination is circa 96% in infancy and circa 90% for the preschool booster [42]. Finally, since the introduction of vaccination may force pathogens to adapt towards a phenotype that best fits its present environment [43, 44], we attempted to interpret clinical surveillance data in relation to changes observed in phenotypic or genotypic characteristics of *B. pertussis* (pathogen surveillance).

This thesis is divided in four parts. In the first part (chapters 2 to 4) we describe the disease burden of pertussis. Chapter 2 comprises a study of the impact of the introduction of the preschool booster. In chapter 3, we evaluate the burden of disease in monetary terms, and in chapter 4 the association between pertussis in infancy and health outcomes on toddler age is studied. In the second part (chapters 5 and 6), we estimate the infection frequency of pertussis, based on serological studies in pregnant women (chapter 5), and more widely in the general population (chapter 6). The third part of this thesis (chapters 7 and 8) comprises studies on transmission routes for pertussis. In chapter 7, transmission routes are studied by looking at age-specific seasonal trends in the occurrence of pertussis, and chapter 8 describes the results of a household study on the transmission of pertussis to infants. Finally, in view of future vaccination strategies, we discuss the possibilities of maternal vaccination to prevent pertussis in infancy (chapter 9), and we consider ways to optimize protection of the population against pertussis (chapter 10, general discussion).
All studies in this thesis were performed within the Centre for Infectious Disease Control of the RIVM and represent a collaboration between the Epidemiology and Surveillance unit and the Laboratory for Infectious diseases and Screening.

References