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

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Summary
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Pertussis is a highly contagious infectious disease of the respiratory tract, which can cause paroxysmal coughing lasting for more than a month, often associated with inspiratory whooping and/or post-tussive vomiting. Before childhood vaccination against pertussis was introduced in the 1950s, pertussis was a major cause of infant death, with 350 deaths per year in the Netherlands. Vaccination successfully decreased the morbidity and mortality due to the disease. However, in 1996 a resurgence of pertussis was observed in the Netherlands despite more than 40 years of programmatic vaccination with a high coverage (chapter 1). Since then, the incidence of pertussis has remained high with between 3,000 and 10,000 reported patients annually and around 200 hospitalisations predominantly involving young children. Still, these figures represent the ‘tip of the iceberg’ as the majority of infections are mild and often go unrecognized, especially in adolescents and adults. In infants, however, infection is most severe and complications may develop, such as pneumonia, encephalopathy or even death.

Routine vaccination against pertussis was introduced in the Dutch National Immunization Programme in the 1950s with a combined diphtheria, pertussis, tetanus and polio (DTP-IPV) vaccine at 3, 4, 5, and 11 months. Due to the re-emergence of pertussis several changes in vaccination strategy were implemented in the last decade: in 1999 the vaccination schedule was accelerated and the first dose of pertussis vaccine is now given at 2 months instead of 3 months of age, in 2001 a preschool booster was introduced for four-year-olds, and in 2005 the Dutch whole-cell vaccine was replaced by an acellular vaccine. Whole-cell vaccines are based on killed and detoxified bacteria, whereas acellular vaccines consist of several purified antigens of the causative organism *Bordetella pertussis*.

The National Institute for Public Health and the Environment (RIVM) monitors and investigates the effectiveness, safety and reliability of (changes in) the National Immunization Programme by means of surveillance. Trends in the occurrence of pertussis are studied by means of disease surveillance and immunosurveillance. Since widespread vaccination may force pathogens to adapt to vaccine-induced immunity, trends in the epidemiology are interpreted in relation to changes observed in phenotypic or genotypic characteristics of *B. pertussis*.

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. Results from studies on the disease burden (chapters 2-4), infection frequency (chapters 5-6), and transmission routes (chapters 7-8) for pertussis are used to recommend optimal vaccination strategies (chapters 9-10) to decrease the burden of pertussis in the Netherlands.
Burden of pertussis

In chapter 2, we determined the impact of the preschool booster for four-year-olds on the burden of pertussis. We showed that the incidence of hospitalised and reported pertussis cases significantly decreased among the targeted population. Another important finding of our study was the decreasing trend in the incidence of pertussis in infants, suggesting that transmission from siblings to susceptible infants was reduced after introduction of the preschool booster. In contrast to the reduction in infants, in the same period the incidence of reported cases among cohorts aged 10-19, 20-59, and ≥60 years, increased with 60%, 44%, and 68%, respectively. Despite the substantial reduction in the number of cases in childhood, the preschool booster was not considered cost-effective (chapter 3). By studying age-specific health care utilization and costs associated with pertussis, we found that the economic burden of pertussis is largely determined by costs per infant case (€1,491) and only to a limited degree by costs per patient in other age-groups (circa €75). Thus, costs of pertussis in adolescents and adults are relatively limited, and prevention of pertussis in infants will be the most effective way to save expenses.

More importantly, from a public health point of view, young infants suffer from the most severe form of disease. Besides, severe pertussis in infancy may have consequences on the long term. In chapter 4, we studied whether there is an association between pertussis in infancy and respiratory and cognitive disorders in early childhood. We compared a group of 89 children aged 13-45 months and hospitalised for laboratory confirmed pertussis within the first six months of their life, with 172 age-matched children without a history of pertussis. Children with a history of pertussis more often showed “asthma like symptoms” on toddler age and were more likely to report “respiratory infections”. Although it is unclear whether there is a causal relation between pertussis infection in infancy and respiratory illness in childhood, this deserves further attention.

From chapters 2-4 we conclude that while vaccination has successfully reduced the pertussis disease burden in childhood, the number of pertussis cases in adults is growing. The latter increases the infection pressure in infants and thus will have a negative impact on the efficacy of childhood vaccination. This emphasizes the need for further measures to prevent severe pertussis in young infants, either by interrupting common routes of transmission or by improving infant immunity to pertussis.

Infection frequency

Surveillance artifacts such as increased awareness and improved diagnostics may have contributed to the observed increase of reported pertussis. The frequency of pertussis infection is most reliably estimated on the basis of the prevalence of high IgG concentrations against pertussis toxin (IgG-Ptx), which is not affected by these surveillance artifacts.
Since mothers suffering from pertussis at the time of delivery have a high chance of infecting susceptible newborns, in chapter 5 we determined the prevalence of infection in pregnant women. In total, 20 (6.3%) of 315 pregnant women in our study showed serological evidence of *B. pertussis* infection during or shortly before pregnancy, which is much higher than the incidence of reported cases in this age group as shown in chapter 2. To study the age-specific infection frequency in the general population, a cross-sectional population-based serosurveillance study was conducted in 2006-07 (chapter 6). For 7,903 participants serum antibody concentrations were analysed and the age-specific seroprevalence (0-79 years) was compared with the seroprevalence obtained from a similar national survey conducted in 1995-96 and with incidence rates calculated from mandatory notifications in both periods. In 2006-07, 9.3% of the population in the Netherlands above 9 years of age had a pertussis infection in the past year, indicating at least a twofold increase compared to the 1995-96 survey (4.0%). Interestingly, the seroprevalence followed a similar trend as the reported incidence between both periods. Obviously, trends in notifications reliably reflect changes in the circulation of pertussis.

**Transmission routes**

To gain insight in pertussis disease dynamics and common routes of transmission, we studied the age-specific long-term periodicity and seasonality of pertussis in the Netherlands (chapter 7). The concurrent annual fluctuation of pertussis incidence that we found in adults and young children, suggests frequent transmission within and between these age groups. This finding was confirmed by the results of a household transmission study named BINKI (which is an acronym in Dutch for: Baby’s geINfecteernd met Klnkhoest) in which we aimed to identify the most likely sources of pertussis infection in young infants (chapter 8). A total of 560 household contacts of 164 infants hospitalized for pertussis were examined by polymerase chain reaction, culture, and serological testing to establish *B. pertussis* infection. Of the household contacts, 53% had laboratory-confirmed pertussis. The most likely source of infection in the infant was a sibling (41%), mother (38%), or father (17%). These data show that selective vaccination of people in close contact with infants (cocooning strategy) will likely reduce transmission of pertussis to infants. Since expectant parents have regular contact with health care and will be well motivated to protect their child, cocooning seems a feasible strategy and its implementation needs urgent consideration on the short term.

**Future vaccination strategies**

Current vaccines only induce transient protection against pertussis and after a few years the risk of (transmission of) infection recurs. Therefore, in chapter 9, we discuss the possibilities...
of maternal vaccination in order to directly improve immunity of infants against pertussis. By placental transfer of maternal antibodies, vaccination in the third trimester of pregnancy may confer protection from the moment of birth. However, due to ethical, technical, and legal dilemmas it is problematic to investigate the efficacy and safety of this strategy in clinical trials.

Finally, in the general discussion of this thesis (chapter 10), we discuss the most likely causes of the dramatic increase in pertussis incidence in the past decade and propose measures to improve the control of pertussis. In literature, different reasons have been given for the cause of the increase in pertussis in the last decade: increased awareness, improved diagnostics, suboptimal vaccines, waning vaccine-induced immunity and pathogen adaptation. Based on the integration of clinical-, pathogen- and immunosurveillance data we argue that the increase of pertussis in the Netherlands cannot solely be attributed to increased awareness and improved diagnostics. Indeed, the increase in the seroprevalence demonstrates that the circulation of the causative pathogen has also increased. The concurrence in time between the emergence of new pertussis strains and the increase in seroprevalence among adults suggests the pathogen has adapted to hosts with waning immunity resulting in a large bacterial reservoir.

Despite the high prevalence of pertussis in adolescents and adults, pertussis in these groups is relatively mild compared to disease in infants and children. Thus, the aim of pertussis vaccination should be to eliminate severe disease and death among infants and young children. The preschool booster and the replacement of the Dutch whole-cell vaccine by an acellular vaccine have successfully reduced the disease burden in children. However, the increased circulation of pertussis in adults calls for additional interventions such as cocooning to prevent transmission to young infants. Ultimately, vaccines that induce long lasting protection against pertussis should be developed.