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

de Greeff, S.C.

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Main findings
The aim of the Dutch National Immunization Programme is to protect the population and society against severe infectious diseases by means of vaccination [1]. Despite more than 50 years of programmatic vaccination with a high coverage (circa 96%), pertussis is still endemic in the Netherlands. Since 1996, the reported number of patients varied every year between 3,000 (i.e., 18 per 100,000 persons) and 10,000 (i.e., 60 per 100,000 persons) and these figures represent the ‘tip of the iceberg’ as the majority of infections go unrecognized. Each year, approximately 200 patients - predominately young unvaccinated infants - are hospitalised and on average one death due to pertussis is reported [2]. The preschool booster vaccination, introduced in 2001, caused a significant decline in the incidence of pertussis among the targeted population and resulted in a reduction in infant morbidity (chapter 2). The shift to an acellular vaccine in 2005 has decreased morbidity in 1-2-year-olds and resulted in a reduction of the number of side effects due to vaccination [3, 4]. However, the number of infections in adults more than doubled in the past decade (chapters 2 and 6). Although the majority of adult infections are mild or subclinical, the high circulation of $B. pertussis$ infections poses a significant risk of transmission to unprotected newborns in whom infections often lead to severe disease and possibly long term sequelae (chapters 4 and 8).

Understanding the disease dynamics and control of pertussis is challenging experts in the field of epidemiology, microbiology, mathematical modelling, immunology and medicine. Studying pertussis disease dynamics is complicated by the lack of specific symptoms in most of the infected persons, especially in adolescents and adults (chapters 6 and 8), making pertussis diagnosis problematic. Control of pertussis is hampered by the fact that there is no accurately defined correlate of protection [5, 6].

The studies presented in this thesis were designed to provide insight in the epidemiology of pertussis in the Netherlands in the past decade and to identify ways to optimize protection of the population, in particular infants, against pertussis. Based on our studies, I will first discuss what I believe are the most likely causes of the dramatic increase in pertussis incidence. Finally, I will propose a number of measures to improve the control of pertussis in the Netherlands.

Explanations for the trends in epidemiology
Increased awareness and improved diagnostics
Since morbidity [7-9] and mortality [10] are generally underestimated in routine surveillance systems, increased awareness leads to a larger part of patients being identified and/or reported. The large variation in reported incidence of pertussis in Europe (e.g., in 2007 the reported...
incidence was 115/100,000 in Norway; 44/100,000 in the Netherlands; and 1.7/100,000 in Denmark) rather reflects differences in awareness, reporting and diagnosis than only differences in vaccination history and population immunity [11]. In the Netherlands, increased attention to pertussis in (medical) journals after the epidemic in 1996 and subsequent changes in the vaccination schedule, will have increased the index of suspicion among clinicians for pertussis in patients with prolonged cough. Interestingly, a dramatic increase of the reported incidence of clinical pertussis cases has also been observed in many other countries, despite a high vaccination coverage [5, 12-15]. Since it is unlikely that awareness improved in a similar way at the same time in different countries, better awareness alone cannot explain the simultaneous resurgence of the disease.

Improved diagnostics is often put forward in literature as explanation for the resurgence of pertussis. In the Netherlands, serological tests for pertussis were exclusively performed at the RIVM before 1996, but since 1998 other laboratories have started to perform serology with commercial available assays. This decentralization may have facilitated pertussis diagnosis resulting in more reliable (and higher) notification rates. The impact of a more wide-spread use of PCR as a diagnostic method is negligible, as only 5% of notified patients is confirmed by PCR each year.

Although the above mentioned changes will have contributed to the observed increase in reported pertussis, the significant increase in the seroprevalence (chapter 6) especially among adults, indicates the true number of infections has also increased. Consistent with this, incidence rates of hospitalisations - which are less affected by changes in clinical practice and diagnostic methods – have also increased among adolescents and adults (chapter 2).

Suboptimal vaccines, waning immunity and pathogen adaptation

I propose the increase in the number of infections in the last decade may be the compound effect of suboptimal vaccines, waning immunity and pathogen adaptation. Estimations of vaccine effectiveness in 1-year-olds show that the VE was above 90% in 1989-1993, and decreased to 30% in 1996-1998 [16]. The use of a suboptimal vaccine [17], is likely to have resulted in a cohort of susceptible children and an increased circulation of the causative pathogen. This is illustrated by a shift of the peak incidence from infants towards preschool children and an increase in incidence over a broad age-range in 1996.

Concurrently, changes in circulating B. pertussis strains were observed. Variations of genes coding for pertactin and pertussis toxin were demonstrated that differed from the vaccine type strains [18] and this mismatch affected vaccine efficacy in a mouse model [19-21]. Besides, a change has been observed with respect to the promoter for Ptx (ptsP) which is a major
virulence factor and component of all pertussis vaccines [22]. The majority of strains isolated since 1996 (\textit{ptxP3} strains) appear to produce more pertussis toxin. Pertussis toxin suppresses the immune response and thus an increased production may enhance virulence [22-24]. The concurrence in time between the emergence of \textit{ptxP3} strains and the shift of disease towards older age-categories, suggests a causal relationship (Figure 1). By increasing suppression of host immune defences, these more virulent strains may be able to infect at higher levels of host immunity, decreasing the duration of vaccine-induced immunity. This assumption is supported by the increased seroprevalence and a growing number of symptomatic infections in adults (this thesis). Apparently, \textit{B. pertussis} has adapted to hosts with waning immunity in order to maintain a bacterial reservoir in a population with high vaccination coverage.

\textbf{Figure 1.} Incidence of notifications and hospitalisations for pertussis per 100,000 persons per year, and the prevalence of \textit{ptxP3} strains in the Netherlands, 1989-2008.

\textbf{Importance of integration of surveillance data}

As has been clearly demonstrated for pertussis, understanding the epidemiology of vaccine-preventable diseases requires the systematic collection and integration of data on clinical cases, seroprevalence, and strain variation.

The combination of notifications and seroprevalence is required to give insight in underreporting and the (changes in) severity of infections. Although the true number of pertussis infections is more than 100 times higher than the reported number of infections (chapter 6), underreporting does not invalidate monitoring the impact of vaccination by trend analysis of the number of clinical cases. Studying clinical surveillance data has increased our knowledge on pertussis and
has directly contributed to the implementation and evaluation (chapter 2) of control measures such as the preschool booster [17]. The notification system is currently the only surveillance system available to monitor trends in the incidence according to the vaccination status of cases. Given the changes in the vaccination programme in recent years and the upward trend in pertussis notifications (chapter 6), the current system of notifications should therefore be continued. Surveillance of hospitalisations registered by the National Medical Register is also of utmost importance as hospitalisations are less subject to surveillance artefacts and therefore allows better comparison of pertussis disease burden between countries.

In chapter 6, we showed that significant changes in the age-specific prevalence of high anti-Ptx IgG levels in a ten year period, agree with trends observed in reported incidence of pertussis at the time. To monitor trends in circulation of the pathogen in the short term, opportunistically collected samples (e.g., from blood donors or residual sera) could be tested for the concentration IgG-Ptx. Ideally, to gain insight in the occurrence of (mild) infections and possibly to find a correlate of protection, a random cohort (preferably also followed for other study purposes) of persons stratified by age and duration since last vaccination could be requested to keep a diary on pertussis related symptoms and coughing contacts, and to give blood every three months in order to assess their concentration pertussis related antibodies (i.e., antibodies against Ptx, Prn, Fim, FHA).

Strain surveillance is required to assess whether increases in notification are due to changes in vaccine quality or changes in the pathogen population [25]. Further, by studying the nature of the changes in the pathogen population, interventions can be proposed [26]. Since culture has almost completely been replaced by serology and PCR as method of laboratory confirmation, it is highly recommended that a (sentinel) system is set up that allows the systematic collection of Bordetella strains, preferably not only from the Netherlands but also from abroad. Since acellular vaccines confer no protection against B. parapertussis infections [27-30] - which can cause similar symptoms as B. pertussis [31, 32] - the occurrence of B. parapertussis infections should also be monitored.

**Implications of the increased circulation for public health management**

In chapter 8, we showed that only 9% of infected household members was treated with antibiotics before onset of illness in the infant and only one of the 164 investigated families received prophylactic treatment confirm the recommendations [33, 34]. This indicates that many general practitioners (GPs) do not recognize pertussis in adolescents and adults or do not acknowledge the potential severity of infection in young infants. Besides typical pertussis symptoms, many adult patients present to their GP with lack of sleep due to
paroxysmal coughing, sweating attacks and cold symptoms [9]. General practitioners should actively ask patients with persistent cough for minimal one week in combination with one of the above symptoms, whether he or she has contact with infants or pregnant women. If the latter is true and suspicion for pertussis is high, for instance as multiple cases in one practice are found, promptly start of antibiotic treatment should be considered [34]. Early diagnosis and treatment of pertussis can prevent severe pertussis in infants and limits the spread of the bacterium. Furthermore, it prevents unnecessary medical procedures, such as bronchoscopies, CT scans, or allergy testing, prompted for suspicion of other diseases [35, 36]. As only a fraction of adults with presumptive pertussis infection visits a general practitioner, public campaigns that inform on infection control measures, such as cover-your-cough campaigns, will help to reduce exposure and transmission [37].

Implications for pertussis vaccination policy
Vaccination has had a tremendous impact on the incidence of pertussis. Indeed, after abandoning of pertussis vaccination, incidence rates of reported pertussis in Sweden increased to 3,370 per 100,000 and in Japan an epidemic occurred in 1979 with more than 41 deaths [38, 39]. Conversely, immediately after re-introduction of vaccination in Sweden and Japan, the incidence of pertussis among vaccinated age groups decreased to similar levels as before the period of vaccine withdrawal [39, 40]. The aim of vaccination can be eradication, elimination, or containment of a disease [41]. Eradication is only feasible for diseases where vaccination offers lifelong protection and high vaccination coverage is achieved. Elimination involves achieving a level of immunity within a population, such that an infectious disease has very little scope to proliferate but the pathogen is still present in the population. Containment can be defined as the point at which the disease, although not eliminated, is no longer a significant health problem. With the current pertussis vaccines that induce only temporarily protection against disease severity and transmission, containment or minimization of disease burden will be the maximum achievable. There is however no level defined when containment is reached. 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 switch to acellular vaccines will not affect morbidity in infants too young to be vaccinated. In Canada the switch to acellular vaccines was made already in 1997, but this has had little influence on the incidence in infants below 3 months of age [42]. Moreover, vaccination with acellular vaccines in childhood does not prevent (re-)infection in adulthood as vaccine induced immunity wanes within 6-10 years [43]. Within households, vaccine induced immunity may even wane more quickly: a third of the children in the BINKI-study (chapter 8) who were vaccinated with the
acellular vaccine were again infected within 4 years after completion of the primary series. The ultimate goal of pertussis vaccination should be to eliminate severe disease and death among infants and young children. Therefore, the increased circulation of pertussis (chapter 6), demands for additional intervention measures to prevent severe pertussis in young infants.

Vaccination measures for the short term
Booster vaccinations for adults will reduce the circulation of pertussis and thus transmission to infants. However, adult booster vaccination may not be the most effective strategy to control pertussis. First of all, due to waning immunity repetitive boosting will be required with the current vaccines [44]. Not surprisingly, many published papers in favour of adolescent and adult vaccination are written by authors linked to the pharmaceutical industry. Secondly, repeatedly vaccinating adults is a very labour-intensive and expensive matter and will not likely be cost-effective (chapter 3). In Canada, it took five years to implement a booster programme for adolescents and adults and implementation occurred only after organizing comprehensive educational programmes to convince authorities, health care providers, and the public of the need of such a programme [45]. Thirdly, personal risk perception may be too low in adolescents and adults to consider pertussis immunization [46]. In chapters 6 and 8, we showed that the majority of infections in these groups are relatively mild. Besides, the recently conducted vaccination campaign for HPV illustrated that besides risk perception many other factors determine willingness to vaccinate beyond childhood [47]. Finally, adult infections have always occurred [48], and since disease is relatively mild compared to disease in infants and children it is debatable whether infections in adults are experienced as a public health problem and justify the public investment of general adult booster vaccinations. When transmission remains high, mild infections among adults will be frequent and will boost clinical immunity, making revaccination redundant. To make appropriate decisions about the vaccination of particular target groups, seven criteria have been formulated by the Health Council [49] grouped under five thematic headings: seriousness and extent of the disease burden, effectiveness and safety of the vaccination, acceptability of the vaccination, efficiency of the vaccination, and priority of the vaccination. It is doubtful whether adult vaccination satisfies these criteria.

Instead of general adults booster vaccinations it will be more (cost-)effective to give booster vaccinations only to adults who are in close contact with infants (such as young parents and health care workers taking care of infants) to reduce transmission. Moreover, feasibility of this ‘cocooning strategy’ will be better as young parents are motivated to protect their baby and have frequent contact with health care.
Vaccination measures for the long term

Vaccinating directly after birth or giving the first dose at six weeks of age, may confer earlier protection against pertussis [50, 51]. Research is needed, however, to demonstrate that early induced immunity does not interfere with subsequent vaccinations or results in an impaired immune response against other vaccine components [52, 53]. Ideally, vaccination of mothers during pregnancy is the best option to protect infants from birth until immunity is induced by active vaccination (chapter 9). However, concerns for safety make this strategy almost unrealizable for a disease like pertussis. Although each of these approaches may be effective, the most (cost-)effective way to reduce the pertussis burden is to introduce vaccines which induce long lasting immunity. The vaccines could be improved so that their composition reflects the antigenic make-up of circulating strains and, in particular, they induce Ptx neutralizing antibodies that persist [22].

General conclusion

The studies in this thesis have shown that despite changes in the vaccination programme which successfully reduced morbidity in childhood, the circulation of *Bordetella pertussis* has increased especially in the adult population. In fact, vaccination in childhood may have led to the evolution of more virulent strains and a shift of the reservoir of *B. pertussis* to adults. However, since the disease burden in the adult population seems relatively confined, the main reason for introducing new vaccination strategies should be to prevent severe pertussis in infants who are too young to be protected by vaccination.

Due to integration of clinical, strain, and immune surveillance data, the Dutch pertussis surveillance system is one of the most comprehensive systems, and surveillance and forthcoming studies are conducted without conflict of interest. Based on the results of this surveillance we propose the following recommendations:

- Young parents, and people who have close contact with young infants (such as health care workers taking care of infants) should receive booster vaccinations.
- To justify an eventual introduction of general adult booster vaccinations, the burden of disease in adults in the Netherlands should be determined.
- The potential long term effects of severe pertussis, and of infant pertussis in general, on loss of quality of life should be further investigated.
- Governmental policy makers and critical researches on pertussis should incite vaccine manufactures to invest in new pertussis vaccines that induce long lasting immunity.
At any point in time, the immunity of the population is the compound effect of disease and vaccination experience and thus the recommendations in this thesis are given for the current situation. Since history of vaccination, the vaccines used, the schedule vaccination and the coverage vary from country to country; care should be taken to generalize these recommendations to other countries. In fact, for many developing countries the challenge is simple to achieve high vaccination coverage of timely immunisation for infants [54]. However, the findings generated from the Dutch surveillance may inspire researchers in countries, and hence will contribute to a better control of the burden of pertussis worldwide.

References

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