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Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants?

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ABSTRACT

Background: Pertussis has resurged in the Netherlands since 1996. Several measures, i.e. acceleration of the schedule, introduction of a preschool acellular pertussis booster and change from an infant whole cell to an acellular pertussis combination vaccine were implemented in the National Immunisation Programme to decrease disease burden, in particular among very young infants who have the highest morbidity and mortality of pertussis. Nevertheless, a large outbreak occurred in 2011–2012.
Methods: 1996–2010 was divided in 3-year-periods to assess the impact of the measures taken, using notifications and hospitalisations. These results were compared with 2011–2012. Mean Incidence rates (IRs) per 100,000 were calculated.
Results: Although the measures taken resulted in decreased IRs among the targeted age groups after implementation, overall mean IRs of notifications increased from 32 (1996–2004) to 37 (2005–2010) and 63 (2011–2012). Young infants, not yet vaccinated, did not benefit; during the 2011–2012 outbreak, IR in 0–2-month-olds amounted to 259.6. IR among persons over 9 years of age increased from 6.8 (1996–1999) to 59.1 (2011–2012) For hospitalisations overall mean IRs decreased from 1.95 per 100,000 (1997–2004) to 0.88 (2005–2010) and 0.76 (2011).
Conclusion: The measures taken reduced IRs of notifications and hospitalisations among groups eligible for vaccination, but had no effect on the increasing IRs in adolescents and adults. This trend is also observed in other countries. The high IRs in 2012 in adolescents and adults probably resulted in increased transmission to infants, who are at risk for contracting severe pertussis. Therefore, additional measures to protect this group should be considered.

1. Introduction

Pertussis or whooping cough is characterised by a catarrhal phase which is followed by a phase with persistent paroxysmal coughing. In typical cases, coughing may be followed by inspiratory whooping and vomiting. Pertussis may be complicated by cyanosis, apnoea, pneumonia or seizures. Even encephalopathy or death may occur, albeit infrequently [1]. Severe pertussis usually occurs in young infants. In adolescents and adults pertussis usually has a mild and more atypical disease course [2,3]. Since the 1950s, vaccination programmes have been introduced worldwide. First whole cell pertussis vaccines (WCVs) were used, later, in the 1990s, many western countries switched to acellular pertussis vaccines (ACVs) with a more favourable safety profile [4,5].

Despite constant high vaccine coverage, pertussis has resurged in many countries, including the Netherlands [6–9]. Pertussis was originally defined as a childhood disease, but the largest increase in pertussis incidence is nowadays found in adolescents and adults.

In the Netherlands, pertussis notifications increased suddenly in 1996 and since then remained at a higher level, with additional peaks every 3–4 years [10]. In 2012, a particular high and broad peak in notifications was observed, starting at the end of 2011 and continuing in 2012. In contrast to the usual seasonal pattern with

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peaks in late summer and autumn, the incidence stayed at a high level during winter and spring, and decreased only after August 2012 [11]. In view of the resurgence of pertussis since 1996 in the Netherlands, several measures were taken to reduce disease burden, with special focus on protecting the most vulnerable, not (completely) vaccinated infants. In 1999, an accelerated schedule of the National Immunisation Programme (NIP) was implemented, in which the first vaccination was given at two instead of three months. From November 2001 onwards, ACV was administered to four-year-olds, simultaneously with the booster Diphtheria-Tetanus-Inactivated Poliovirus (DT-IPV) vaccine. Finally, in 2005 the DTP-IPV-*Haemophilus influenzae* type b (Hib) combination vaccine including WCV was replaced by a combination with ACV at 2, 3, 4 and 11 months of age. This article aims to evaluate the impact of these measures on the pertussis burden, using surveillance data on hospitalisations and notifications by law routinely collected since 1975. We discuss the possible impact of additional measures in view of improvement of the control of pertussis, in infants too young to be vaccinated who have the highest morbidity and mortality.

2. Methods and materials

2.1. Notifications

Pertussis is notifiable by law since 1976. In the mandatory reports, among others, information on vaccination status is available. We included data from 1996–2012 since in this period a stable case-definition for notification was used, which includes a clinical picture compatible with pertussis combined with laboratory confirmation of *Bordetella (para)pertussis* infection or contact with a laboratory confirmed patient with a *B. (para)pertussis* infection in the last three weeks. Laboratory confirmation can be based on isolation of the bacterium, detection of DNA by polymerase chain reaction (PCR), a ≥4-fold rise in IgG antibodies against pertussis toxin (Ptx) in paired serum samples, or a single serum sample with IgG-anti-Ptx concentrations above a defined age-specific cut-off value [12]. The relative distribution of diagnoses based on culture or PCR, serology as well as epidemiological linked cases (i.e. ~5%, ~90%, ~5%, respectively) has been stable over the years under study.

2.2. Hospitalisations

Hospitalisation data in the period 1997 to 2011 were retrieved from the National Medical Registration (LMR). LMR collects discharge diagnoses of all patients admitted to the hospital. Only inpatient diagnoses are registered. Diseases are registered as main or side diagnosis according to International Classification of Diseases (ICD-9) coding. Coverage was ~99% until mid-2005; thereafter coverage has fluctuated around 90%. Age specific data were available since 1997. Patient records with code 0330 or 0331 (whooping cough caused by *B. pertussis* and *B. parapertussis*, respectively) and 0338 or 0339 (whooping cough caused by other specified or an unspecified organism, respectively) were included.

2.3. Statistical analysis

To assess the impact of the measures taken, we divided 1996–2010 in five periods of three years (Box 1). Three of the five periods, 1999–2001, 2002–2004 and 2005–2007, coincided with a change in the NIP. We calculated mean incidences per 100,000 for each period, which diminished the influence of peak incidences every 2–3 year; peak years were 1996, 1999, 2001, 2004, 2007 and 2008. To relate these results to the current situation, we also present mean IRs for 2011–2012. For hospitalisations the first period consisted of two years (1997 and 1998) and data on 2012 were not available yet.

Mean incidences were calculated using numerators from the respective registries and age specific denominators, retrieved from CBS (www.statline.nl), being the number of inhabitants in the specific period.

For comparing incidences in different periods or age categories, risk ratios (relative risk, RR) were calculated with 95% confidence intervals (95%CI). Changes were regarded as significant if the 95% CI did not include '1'.

Vaccine effectiveness (VE) was estimated using the 'screening-method' [13].

$$VE = \frac{1 - PCV}{(1 - PCV)} * \frac{1 - PPV}{(1 - PPV)}$$

PCV = proportion of cases vaccinated

PPV = proportion of population vaccinated

For infant vaccinations and the booster dose at four years of age, PPV was set at 96% and 92%, respectively [14]. If PCV exceeded PPV, estimation of VE was not possible.

Calculations were performed using SAS version 9.3, Excel and Episheet.

3. Results

The overall mean incidence per 100,000 of notifications increased from 32 (1996–2004) to 37 (2005–2010) and 63 (2011–2012). For hospitalisations overall mean incidence decreased from 1.95 (1997–2004) to 0.88 (2005–2010) and 0.76 (2011)(Fig. 1).

Age specific incidences fluctuated over time with peaks every 2–3 years in the period 1996–2004 (Fig. 2A and B). After the peak in 2004, for those of 4–6 and ≥10 years as well as those 0–2 months of age peaks occurred in 2008, with the largest peak occurring in the young infants. For the age groups 3 months to 3 years of age a decreasing trend was observed from 2004 until 2010–2011 with no discernible peaks. Thereafter, an increase was seen again.

Box 1: Overview of used schedules and vaccines in the defined periods.

1996–1998	1999–2001	2002–2004	2005–2007	2008–2010	2011–2012
Infant WCV[a]	Infant WCV[a]	Infant WCV[a]	**Infant ACV[b]**	Infant ACV[b]	Infant ACV[b]
Start NIP 3 m	**Start NIP 2 m**	Start NIP 2 m	Start NIP 2 m	Start NIP 2 m	Start NIP 2 m
No booster 4 year	No booster 4 year	**ACV[c] booster 4 year**	ACV[c] booster 4 year	ACV[c] booster 4 year	ACV[c] booster 4 year

Changes between successive periods are in bold.

[a] DTwP-IPV (+Hib) vaccine/RIVM + NVI.

[b] From January 1st 2005 til December 31st 2005, Infanrix-IPV-Hib/GSK was administered during infancy. From January 1st 2006 till 2008, Pediacel/SP MSD was administered. From 2008 onwards Pediacel was gradually replaced by Infanrix-IPV-Hib again. From October 1st 2011 onwards all infants received Infanrix hexa/GSK.

[c] Untill July 2006 single aP/GSK was used as a booster. From August 2006 till 2008, Triaxis Polio/SP MSD was administered. Thereafter, this was gradually replaced by Infanrix-IPV/GSK.