



Pertussis in infants under one year old: Risk markers and vaccination status—A case-control study



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ABSTRACT

Background: Pertussis is a contagious bacterial disease causing substantial health burden. Pertussis-related morbidity and mortality are highest in young infants. We investigated risk markers for pertussis and vaccination status in infants.

Methods: Reported pertussis cases under one year old during 1998–2011 in the Jerusalem district were matched to controls by birthdate and residence. Data sources included epidemiological investigations, health records and vaccination records (number and dates of DTP\DTaP doses scheduled at 2, 4, 6 months). Vaccine effectiveness was calculated by number of vaccine doses stratified by age group. Timeliness of vaccine doses was also evaluated.

Results: The study population included 1268 infants under 1 year: 317 pertussis cases and 951 age-matched controls (mean age 3.95 ± 3 , median 2.9 months). Low birthweight (<2500 g, 12.3% in cases vs. 6.3% in controls) and high birth order (4th and above) were found to be independent risk markers. Male gender and low socio-economic status were more frequent among cases. Some 40% of the cases (127/317) were hospitalized, most of them (111/127, 87.4%) were under 4 months (mean age 2.42 ± 2.05 , median 1.8 months).

The distribution of the number of pertussis vaccine doses 0, 1, 2 and 3 differed considerably being 42.2%, 32.7%, 15.6%, 9.5% vs. 13.7%, 41.9%, 22.9%, 21.5% among cases and controls ($\geq 2m$), respectively. The overall vaccine effectiveness found was 72.9%, 76.1% and 84.4%, for the 1st, 2nd and 3rd doses of a pertussis vaccine. The infant's age at the first dose of pertussis vaccine was recorded with follow-up until age 18 months. Delay was more common among cases with a lower proportion vaccinated—78.9% at 18 months vs. 99% in controls.

Conclusions: Specific risk markers for pertussis in young infants were identified. Reported pertussis cases over age 2 months were significantly more likely to be unvaccinated and have delayed vaccinations. The vaccine effectiveness increased with the number of vaccine doses.

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1. Introduction

Despite being a vaccine preventable disease for decades, pertussis is still a major cause of morbidity and mortality worldwide. An increase in reported pertussis incidence over the last two decades has been observed in many developed countries [1–6]. Pertussis-related burden is considerable in childhood. In 2008 pertussis accounted for 2% of the mortality among under-5-years old

children globally with an estimated 195,000 deaths [7]. The peak age-specific incidence rate of pertussis has been reported in infants younger than one year, mainly in the first months of life. [7,8]. Aiming to protect young infants, several public health strategies have been utilized e.g. booster pertussis vaccinations for schoolchildren and adolescents, vaccinating pregnant women, vaccinating parents and household members (cocoon strategy) and vaccinating newborns [9–14].

The reported pertussis incidence in Israel increased from 1 to 2/100,000 population in 1994–1998 to 37/100,000 in 2007. The incidence increased predominantly in infants under one year and children aged 5–14 years [15,16]. The increase in pertussis incidence was attributed primarily to waning of vaccine-induced immunity and additionally to increased physician awareness and availability of sensitive diagnostic tools [15,16]. In Israel, the whole

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cell pertussis vaccine (wP) was introduced in 1957 (at 2, 4, 6 and 12 months) and replaced with acellular pertussis vaccine (aP) in 2002. The mean national immunization coverage at age two years was stable in the last decade at 93–94%. [15,16]. Booster vaccine doses were introduced in schoolchildren in 2005 (age 7–8 years, second grade) and 2008 (age 13–14 years, eighth grade). During 2009–2010, a decline in pertussis incidence has been observed among children aged 5–9 years (61.5%) and 10–14 years (73.9%), with no similar trend among infants [17]. The pertussis incidence rate in infants increased fivefold in 2011, compared to the mean incidence in 2009–2010 [16,18]. Infants presented the peak incidence rate of pertussis and accounted for 80% of pertussis-related hospitalizations nationally [18,19]. During the years 1998–2011 10 pertussis-related deaths were reported—all in infants [15,18,19].

The substantial burden of pertussis in infants led us to explore risk markers and vaccination history in a case-control study among infants younger than one year.

2. Methods

Infections caused by *Bordetella pertussis* are notifiable in Israel by law, applying both to physicians and to microbiological laboratories who notify cases to the district health office. During the study period, (1998–2011) the case definition for reported pertussis in Israel was clinical pertussis as diagnosed by a physician, with or without laboratory confirmation. The physicians refer patients for laboratory tests based on the clinical presentation (acute cough illness with cough paroxysms, inspiratory “whoop”, post-tussive vomiting, or apnea with/without cyanosis). Laboratory tests included real time polymerase chain reaction (PCR) test for *B. pertussis* (since 2000) and/or serologic tests for immunoglobulin IgA and IgG antibodies to *B. pertussis* by a standardized enzyme-linked immunosorbent assay (ELISA) [20,21]. The case ascertainment was based on clinical presentation and *B. pertussis* laboratory test or epidemiological connection. The epidemiological variables included: age, gender, address, date of disease onset, laboratory tests, hospitalization and close contacts. The Jerusalem district’s population was about 1 million (2011) with infants under one year comprising 2.8% of the population [22]. Live births notifications are included in the district newborn registry. Routine childhood vaccinations are provided in well-baby clinics and immunization data are recorded in computerized health records.

2.1. The case control study

A case was defined as an infant under one year of age reported with pertussis during 1998–2011. Three controls per case were randomly selected from the newborn registry. Controls were matched by birthdate and residence in the district. The controls were checked against the notifications to ensure that they were, indeed, not reported on as pertussis cases. The variables obtained from the newborn registry included age, gender, address, birthweight, birth order, maternal age and country of origin. Socio-economic status was assessed by the fraction of families exempted from municipality taxes in the neighborhood. Vaccination data and dates of vaccine doses were obtained from the computerized health records in the vaccinations registry [23]. The routine vaccination schedule includes three pertussis vaccine doses at ages 2, 4, 6 months and a 12 months booster in a combined diphtheria–tetanus–acellular pertussis–Polio–Haemophilus influenzae B (DTaP–IPV–Hib) vaccine. The whole cell pertussis vaccine (wP) had been replaced with acellular pertussis vaccine (aP) in 2002. The vaccination status was defined as up-to-date as per the number of pertussis vaccine doses received in line with the recommended schedule prior to the date of disease onset. The study was conducted in accordance with the

ministry of health instructions and approved by the ministry of health institutional ethical review board.

2.2. Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences, SPSS® software [24]. Continuous variables were compared by Student *t* test and dichotomous variables by Pearson chi-square test. Medians were compared by Independent Samples Median Test. Extended Mantel–Haenszel test was used for trends. Seasonality was evaluated by Ratchet circular scan test (3-month peak). Odds ratio (OR) and 95% confidence intervals (95%CI) are presented. A conditional logistic regression model was used for risk markers and vaccination status between cases and controls. Vaccine effectiveness (VE) was calculated as 1 minus the adjusted OR from the conditional logistic regression model. VE was assessed in hospitalized and non-hospitalized cases and according to ascertainment of cases (laboratory vs. clinical-epidemiological). VE was also estimated for the three time-periods (‘wP vaccine period’ 1998–2001, ‘aP vaccine period’ 2002–2010 and ‘epidemic year’ 2011). The timeliness of the first dose of pertussis vaccine was compared in cases and controls and plotted by inverse Kaplan–Meier curve. A *p*-value <0.05 was considered significant for all comparisons.

3. Results

During the years 1998–2011 a total of 2197 pertussis cases were reported in the Jerusalem district (mean annual incidence rate 18 ± 13.4 per 100,000). Infants younger than one year presented the highest age-specific mean incidence rate of pertussis (96/100,000) compared to other age groups. The annual incidence rate in infants increased abruptly from 64.6/100,000 in 2009–2010 to 399/100,000 in 2011. Infants under one year, children under age 5 years and under 15 years comprised 14.4% ($n = 317$), 27% ($n = 592$) and 65.4% ($n = 1436$) of reported pertussis cases, respectively. Of the 317 infants, 247 (77.9%) were under 6 months and 70 (22.1%) were 6–11 months old (representing 11.2% and 3.2% of all reported pertussis cases).

The study population included 317 reported pertussis cases in infants younger than one year and 951 age-matched controls. Of the 317 pertussis cases, 42 cases occurred during 1998–2001 (‘wP vaccine period’), 169 cases during 2002–2010 (‘aP vaccine period’) and 106 cases in 2011 (‘epidemic year’). The three-month peak period of pertussis was observed in April–June (Ratchet circular scan test, $p < 0.005$).

Most cases were younger than 6 months of age with 106 (33.4%) under 2 months and 90 (28.4%) aged 2–4 months (Fig. 1). Among infants under 2 months the distribution of ages 0–0.5 month, 0.5–1 month, 1–1.5 month and 1.5–2 months was: 6 (5.7%), 20 (18.9%), 41 (38.7%) and 39 (36.8%), respectively. The youngest infant reported was a 5 days old newborn whose mother was diagnosed with pertussis at the time of delivery.

During the study period, 150 notified pertussis cases (all ages) in the district required hospitalization, 127 (84.7%) of them were infants under one year. Most hospitalized infants (87.4%) were younger than 4 months vs. 44.8% of non-hospitalized infants (Fig. 1). The hospitalization rate declined with age; 75.9%, 61%, 46.7% and 13.2% in 0–1, 1–2, 2–4 and 4 and above months, respectively (p for trend = 0.0001). The main clinical signs in hospitalized infants were cough (94%), cyanosis/desaturation (72%) and apnea (33%) and the average hospital stay was 6 ± 3.5 days. One hospitalized infant, a two month-old, (unvaccinated as to age) died due to severe respiratory insufficiency. The case ascertainment differed, being PCR test, serologic tests, culture and clinical-epidemiological in 70.2%, 21.3%,

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