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Risk factors of ICU or high dependency requirements amongst hospitalized pediatric pertussis cases: A 10 year retrospective series, Singapore

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ABSTRACT

Introduction: Pertussis causes the highest complication rates and deaths in the infant group. Our study explored risk factors for ICU/high dependency (HD) admissions and intubation/non-invasive ventilation (NIV).

Methods: A retrospective review of pertussis admissions over 10 years from 2007 to 2016 was done at KK Women's and Children's Hospital, Singapore. To understand risk factors for severe pertussis infection, we compared cases requiring ICU/HD care with controls admitted to the general ward. Risk factors for intubation/NIV were also studied. Vaccine efficacy for protection against ICU/HD admission or intubation/NIV was also calculated.

Results: There were 200 pertussis patients with a median age of 2.75 months. Sixty-one % were ≤3 months and 14.5% were <6 weeks old. Majority of patients (77%) had no prior pertussis vaccination. After removing 3 patients with missing vaccination records, 20 cases were compared with 177 controls. On univariate analysis, risk factors for ICU/HD admission comprised: Age ≤3 months, contact history, underlying co-morbidity, prematurity, absent DTaP vaccination, lymphocytosis, hyperleukocytosis (wbc $\geq 50 \times 10^9$/L), thrombocytosis (platelet $\geq 500 \times 10^9$/L), and pneumonia. Multivariate analysis revealed that age ≤3 months (OR 40, 95% CI 4.57–1111.11, p = .007), co-morbidity (OR 8.46 (95% CI 1.47–56.89, p = .019), pneumonia (OR 18.08, 95% CI 3.22–132.15, p = .002), white cell count (OR 1.07, 95% CI 1.01–1.14, p = .023) and cyanosis (OR 5.09, 95% CI 1.31–24.71, p = .026) were risk factors for ICU/HD admission. Prior DTaP vaccination had a vaccine effectiveness of 86.5% in preventing ICU/HD admission and 82.1% in preventing intubation/NIV.

Conclusions: As the majority of pertussis patients were infants ≤3 months old who are at high risk for ICU/HD admission and intubation/NIV, prevention is key to reducing pertussis morbidity. Even though not statistically significant, DTaP vaccination had a role in preventing ICU/HD admission and intubation/NIV.

1. Introduction

There has been a worldwide resurgence of pertussis cases recently with 16 million cases in 2008 reported by WHO worldwide and 95% occur in developing countries [1]. The reasons for this are multifactorial and include: increased awareness, improved detection methods, reduced potency of acellular vaccines compared to high efficacy whole cell vaccines, waning immunity and ongoing mutations which have resulted in a drift of circulation strains away from those used for vaccine production [2,3]. Immunity to pertussis whether by infection or vaccination is not long-lasting: post-infection protection lasts 4–20 years, post-vaccination: 4–12 years [4].

In Singapore, pertussis vaccination was first introduced in 1959 [5]. In line with global changes, the acellular pertussis vaccine with lower reactogenicity and fewer adverse events replaced whole cell pertussis vaccine in 2007. The national immunization schedule recommends DTaP vaccination to start at 3 months followed by

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further doses at 4 months and 5 months old to complete the primary course. While the vaccine schedule is a national recommendation which is followed by the polyclinics where the majority of infants get vaccinated, private healthcare providers have the liberty to start the DTaP schedule earlier at 6–8 weeks using the 5 in 1 or 6 in 1 vaccines. The first booster DTaP dose is administered at 18 months and second booster Tdap is administered at 11 years old.

The childhood pertussis vaccination program achieved high coverage (>95% for primary doses) and led to significant reductions in pertussis disease burden. An average of 4 pertussis cases per year was reported until 2007 when there was a spike of 38 cases. This sudden increase could be attributed to the implementation of PCR testing in place of the less sensitive and less specific immunofluorescence method at the end of 2006 in our hospital which is the largest provider of women's and pediatric public hospital care in Singapore. In our previous study from 2007 to 2012, there were a total of 98 pertussis patients [6].

Young age <60 days old has previously been established to be a risk factor for ICU admission [7–10]. In this report, we aim to compare the risk factors for severe pertussis requiring intensive care/high dependency (HD) admission against controls admitted to general wards. HD is a unit for escalated care from the general ward without the need for intensive care. It caters for more severely ill patients requiring close observations and monitoring as well as intervention such as non-invasive ventilation (NIV) by positive-pressure ventilation to be administered. It does not cater for patients who require invasive ventilation. In addition, patients who were intubated or received NIV were compared with non-intubated/non-NIV patients. As a secondary outcome, we aimed to explore the vaccine efficacy of any prior DTaP vaccination against ICU/HD admission and intubation/NIV.

2. Methods

This is a retrospective study of pediatric pertussis cases admitted to KKH over 10 years from January 2007 to December 2016. Pertussis was confirmed if it was positive from nasopharyngeal or throat swabs using the PCR method at KKH. The real-time PCR method as described by Kosters et al. was used in the microbiology laboratory at KKH from 2007 onwards [11]. This method targets the insertion sequence IS 481 and the assay was optimized on the Rotogene (Corbett Research, Australia). In addition, an alternative target IS1002 was to confirm presence of *B. pertussis* if required [12]. Patients who were being evaluated for pertussis on admission often had respiratory virus testing by nasopharyngeal swabs using the immunofluorescence (IF) method.

Medical case notes were obtained to extract demographic data, symptoms, signs, contact history, co-morbidity, prematurity including gestational age, vaccination history, type of macrolide used for treatment, type of respiratory support, outcome, other microbiology testing, full blood count and chest X-ray reports as reported by radiologists. Fever was defined as a tympanic or axilla temperature recorded by caregiver or during admission as $\geq$38 °C. Facial congestion was described as the face turning beet- red after a period of prolonged coughing. Vaccination history was obtained from the case notes and verified from the online National Immunization Registry, Singapore for local children. A diphtheria, pertussis, tetanus (DTaP) vaccine dose was counted as valid if it was given 7 or more days prior to onset of illness. Patients with missing vaccine data were removed from the univariate and multivariate analysis. A contact was defined as a household or close contact who was epidemiologically linked to the patient and had a preceding cough prior to the index case. These household contacts were not microbiologically proven to have pertussis. Pneumonia was defined as consolidation or patchy opacities on chest X-ray. When >1 full blood count (FBC) was performed, the highest white blood cell (WBC) count and platelet count was used for analysis. Hyperleukocytosis was defined as WBC $\geq 50 \times 10^9$/l. Thrombocytosis was defined and classified into mild ($500–699 \times 10^9$/l), moderate ($700–899 \times 10^9$/l) and severe ($\geq 900 \times 10^9$/l) [13]. Readmissions were not included into the univariate or multivariate analysis nor the vaccine effectiveness calculations.

While the national schedule starts the primary series at 3 months old, healthcare providers especially in the private sector also provide parents the option to start the schedule earlier at 6–8 weeks usually with the 5 in 1 or 6 in 1 vaccines. Therefore only children below 6 weeks of age who were not eligible for pertussis vaccination were excluded from the secondary analysis of vaccine effectiveness (VE) calculations. VE of pertussis vaccine for ICU/HD admission or intubation/NIV was calculated using the following formula:

$$\text{Vaccine effectiveness (VE)} = (1 - \text{Odds Ratio}) \times 100$$

This study was approved by the Combined Internal Review Board for waiver of consent from patients.

2.1. Data analysis

All statistical analyses were performed using SPSS v 17.0 software (IBM, Armonk, New York). Demographic and clinical characteristics were compared between cases and controls using chi-square test or Fisher's exact test (when numbers were <5) for categorical variables and the student's *t*-test for continuous variables. Logistic regression model with backward variable selection was used for multivariable analysis with specified exit threshold at p-value $\geq$ .10. The demographics and clinically relevant variables, such as age (categorised to $\leq$3 months and >3 months), vaccination status, presence of cyanosis, shortness of breath, cough duration, co-morbidity, positive contact history, prematurity, total white blood cell count, lymphocytosis, thrombocytosis, combined leukocytosis and thrombocytosis and pneumonia were considered as potential risk factors. All tests were two sided at 5% level of significance.

3. Results

There were a total of 200 pertussis inpatients during the study period with a median age of 2.75 months (IQR 1.75–4.25 months, range 2 weeks–18.75 years). Sixty-one % were $\leq$3 months old of which 14.5% were <6 weeks old and 46.5% (n = 93) between 6 week and 3 months old and 54% were males.

The median cough duration was 10 days (interquartile range [IQR] 7–14 days). Fever was present in 11.4% (n = 22) of patients and the median duration was 2 days (IQR 1–4 days). Apart from cough, the most common symptoms were vomiting and facial congestion. The median length of stay was 3 days (IQR 2–5 days). Full recovery was seen in 188 patients (94%), readmissions in 7 patients (3.5%), sequelae in 3 patients (1.5%) and death in 2 patients (1.0%). Reasons for readmission within 1 month of initial discharge were due to issues related to pertussis e.g. ongoing respiratory or feeding issues and 1 of the 7 patients had a total of 3 admissions.

A positive contact history was present in 70.5% (n = 141) of which the following contacts were found: 1 contact: 59.6% (n = 84), 2 contacts: 30.5% (n = 43), $\geq$3 contacts: 9.9% (n = 14). Among a total of 215 known contacts, a positive contact history was reported mainly from sibling/siblings (n = 63, 29.3%) and mother (n = 58, 26.9%). Other positive contact histories included father (n = 36, 16.7%), grandmother (23, 10.7%), grandfather or cousin (n = 8 each, 3.7% each), other relative (n = 13, 6%) or nanny/maid/housemate (n = 6,

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