Changing Patterns of Pertussis in a Children's Hospital in the Polymerase Chain Reaction Diagnostic Era

Sophie Hale, BVSc[1,2], Helen E. Quinn, PhD, MAE[1,2], Alison Kesson, MBBS, PhD[3], Nicholas J. Wood, MBBS, MPH, PhD[1,2,3], and Peter B. McIntyre, MBBS, PhD[1,2,3]

Objective To assess changes in diagnostic practice and vaccine schedules for pertussis, we used culture-confirmation and clinical severity to compare pertussis cases at a single Australian tertiary pediatric hospital during relevant periods.

Study design We replicated the case ascertainment methods of a study reporting a 2-year epidemic period 1997-1999 (whole cell pertussis vaccine with 18-month booster, only culture available) to conduct a retrospective cross-sectional observational study over a 6-year period 2007-2012 (acellular pertussis vaccine, no 18-month booster, polymerase chain reaction and culture available). Cases were compared from case note review 2007-2012 (including prevalence of comorbidities) and published data 1997-1999.

Results During 2007-2012, average annual hospitalizations in those aged <6 months increased 2.3-fold (32.0 vs 14.0) and in those aged >6 months by 5.1-fold (17.7 vs 3.5). Limited to culture-positive hospitalizations, there was no increase in those aged <6 months (14.0 vs 14.5) contrasted with a 4.6-fold increase in those aged >6 months (2.3 vs 0.5), despite increased annual culture requests (488 vs 188). In 2007-2012, significant comorbidities were documented in 41/72 (57%) hospitalized children aged ≥12 months vs 38/225 (17%) <12 months (OR 6.5, 95% CI 3.7-11.7).

Conclusions Increased cases of culture-positive hospitalized pertussis were limited to fully immunized children >6 months of age, consistent with schedule changes. Significant comorbidities were common, making a booster dose at 12-18 months of age especially important. *(J Pediatr 2016;170:161-5)*.

In Australia and the US, acellular pertussis vaccines replaced whole cell pertussis vaccines in the 1990s, and pertussis resurgence has been documented 10-15 years later. In both countries, waning of vaccine effectiveness has been identified in children 7-12 years of age.[1-3] In Australia, where the previous fourth dose at 18 months of age was discontinued in 2003, waning effectiveness also has been documented among children 2-4 years of age.[4] Studies from the US and Australia have suggested that whole cell vaccines provide protection of longer duration than acellular vaccines,[1-3] but the advent of polymerase chain reaction (PCR) testing for pertussis also has changed the landscape. In Australia, PCR augmented or replaced culture as the primary diagnostic method in children, first in hospitalized infants from about 2000, and more recently in children presenting to primary care.[5] Specimens for PCR are more readily obtained, promoting greater use, and PCR is substantially more sensitive than culture, especially in immunized children.[6] The effectiveness of acellular vaccines in preventing hospitalization in the first year of life is high,[4] but little information is available on the relative severity of PCR-diagnosed vs culture-diagnosed cases, or for children who present to hospital with pertussis after 12 months of age. In this study in a single large tertiary pediatric hospital in Sydney, Australia, we replicated the methodology used to report on a previous 2-year period in the whole cell vaccine and culture era (1997-1999),[7] which included a pertussis epidemic, to study a 6-year period, in the acellular vaccine era (2007-2012), which also included an epidemic, but when PCR testing, as well as culture, was available for diagnostic testing. We aimed, by comparing case data from the same institution with consistent criteria for use of culture for diagnosis, to better evaluate the impact of 2 significant changes between these 2 time periods: first, replacement of whole cell by acellular vaccines and second, discontinuation of the booster dose at 18 months of age.

Methods

The Children's Hospital, Westmead, is a 250-bed tertiary care pediatric teaching hospital in Sydney, New South Wales. A retrospective cross-sectional

ED	Emergency department
ICD	*International Classification of Disease*
ICU	Intensive care unit
PCR	Polymerase chain reaction

From the [1]National Center for Immunization Research and Surveillance of Vaccine Preventable Diseases, [2]Discipline of Pediatrics and Child Health, University of Sydney, and [3]Department of Microbiology and Infectious Diseases, The Children's Hospital at Westmead, Westmead, New South Wales, Australia

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observational study was performed by medical record review of pertussis cases identified during a 6-year period (January 2007 to December 2012), using information on both laboratory testing and discharge coding. Eligible cases were those coded by *International Classification of Disease* (ICD) discharge codes as whooping cough because of *Bordetella pertussis* (ICD 10 A37.0) or whooping cough, organism unspecified (ICD 10 A37.9), as well as any child with laboratory proven pertussis through positive culture, PCR (IS481 primers) or serology (Novagnost IgA Enzyme-linked Immunosorbent Assay; Siemens Healthcare Diagnostics, Eschborn, Germany), including both hospitalized children and those seen only in the emergency department (ED). The study was approved by The Sydney Children's Hospital Network Human Research Ethics Committee.

Clinical data for eligible cases was obtained from the Children's Hospital, Westmead electronic medical records database. Clinical features and outcomes at both initial presentation and during hospitalization, as recorded in inpatient notes or discharge summaries, were entered into a database. These included paroxysmal coughing, inspiratory whoop, posttussive vomiting, fever (>38°C), episode(s) of apnea and/or cyanosis, admission to intensive care unit (ICU), and assisted ventilation. Data on investigations included testing for, and identification of, coinfection with respiratory viruses, and chest radiograph reports for consolidation or other acute abnormality. Level of care was classified in 3 categories of severity: ED visit only, hospital inpatient care, stratified into admission for <2 days and ≥2 days, and intensive care, stratified by requirement for assisted ventilation. Chronic comorbidity was defined as preexisting medical condition(s) requiring regular medical follow-up. Comorbidities where further subcategorized as cardiorespiratory, conditions associated with immunodeficiency (such as hematologic malignancy), chromosomal abnormalities, and "other". Prematurity was defined as a gestational age <37 weeks, with extreme prematurity defined as a gestational age <28 weeks.

Vaccination Status

Immunization history was obtained from the Australian Childhood Immunization Register, which contains information on vaccines given to children born since January 1996, who are registered in the national health insurance database, and for whom vaccination encounters have been reported by a vaccine provider to the Australian Childhood Immunization Register.[8] A child was considered to have received a valid dose of pertussis antigen-containing vaccine if administered at least 14 days before presentation.

Comparison with 1997-1999 Study

For the 2 years (1997-1999) of the original study, we did not have access to individual case notes and relied on published data for diagnostic testing, age, and hospitalization status.[7] In the 1997-1999 study, immunization history was obtained from clinical notes for inpatients and was not available for outpatients.

Statistical Analyses

Proportions and medians were reported where appropriate; statistical significance was assessed using either a χ^2 test or Mann-Whitney test, with a P value of <.05 considered statistically significant. The strength of association between variables was measured using an OR with 95% CIs.

Results

In 2007-2012, 3731 children had pertussis PCR performed (average 623 per year), with 519 (14%) positive and 2925 also had culture performed (average 488 per year), with 126 (4%) positive. No PCR-negative cases were positive by serology or culture. In addition to the 519 cases identified by PCR with or without culture confirmation, there were 2 who had positive serology and no additional investigations and another 36 who had ICD discharge codes for pertussis (33 PCR negative; 3 not laboratory tested); giving a total of 557 pertussis cases of whom 36 (6.5%) were not laboratory confirmed.

Demographic Characteristics, Level of Care, and Immunization Status in Laboratory Confirmed Cases, 2007-2012

Figure 1 (available at www.jpeds.com) shows cases for the period 2007-2012. Of 521 laboratory confirmed cases, 298 (57%) were hospitalized, with 55 (18%) requiring ICU; 223 (43%) were managed solely in the ED. Children <12 months of age accounted for 76% of hospital admissions; 74% were of at least 2 days duration and of these, 20% included a period of ICU admission. Although children aged ≥12 months represented only 24% of those hospitalized, severity was high (at least 2 days for 60% and ICU in 13%). Hospitalized cases had a median age of 3.2 months (IQR 1.5-10.9), significantly younger than those managed solely in the ED (28.7 months; IQR 0.7-203.9; $P < .05$). Cases admitted to ICU had a median age of 2.3 months (IQR 1.0-6.9), significantly younger than other hospitalized cases (3.3 months; IQR 1.7-12.7; $P < .05$).

Among cases aged <12 months, the proportion who had received no pertussis vaccine doses decreased from 100% for those aged <2 months to 3% among hospitalized infants aged 6-11 months and 13% among ED managed infants aged 6-11 months. Among those aged 6-11 months, 23% of hospitalized cases and 71% of ED managed cases had received 3 doses at least 14 days previously. In contrast, among hospitalized cases aged ≥12 months of age, 83% had received at least 3 doses of pertussis vaccine, slightly lower than the ED-managed cases with 94%. Among hospitalized infants <12 months of age, those who had received ≤1 dose of pertussis containing vaccine were more likely to be culture-positive than those who had received at least 2 doses of vaccine (OR 8.7, 95% CI 2.5-29.9).

Comorbidities, Age, and Level of Care, 2007-2012

Among hospitalized cases, the proportion with a comorbidity present increased from 11%-15% for those aged <6 months