

# PERTUSSIS IN INFANTS: HOW TO PROTECT THE VULNERABLE?

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## Abstract

In terms of adverse outcomes, infants remain the group most vulnerable to severe pertussis disease. Adult household contact is thought to be the main source of transmission to infants. This study reviews exposure history, vaccination status, admission outcome and quality of discharge coding of hospitalised infants with pertussis at a tertiary paediatric hospital. We identified cases between 1997 and 2006 from 2 sources: hospital discharge coding and positive *Bordetella pertussis* results from the hospital laboratory database. We assessed the completeness of each of these sources, compared with the dataset of all identified cases. We identified 55 hospitalised infants with pertussis. The 35 cases (64%) less than 3 months of age had greater risk of Intensive Care Unit admission, higher mortality, and were more likely to have parents as an identified source. On admission, only 5 cases (9%) were more than 2 weeks overdue for their previous scheduled pertussis vaccination. Discharge coding was more sensitive for identifying cases than the laboratory database. Nine cases (16%) had incorrect discharge coding. Even infants up to date for pertussis vaccine can have severe disease requiring hospitalisation. Immunising parents planning to have, or who have had, a newborn baby may help to prevent pertussis in infants. *Commun Dis Intell* 2008;32:449–456.

Keywords: whooping cough, *Bordetella pertussis*, infants, household transmission

## Introduction

Infants are the group most vulnerable to severe pertussis disease, with higher rates of hospitalisation and death. Acellular pertussis vaccines replaced locally produced whole-cell vaccine in a primary course of vaccination at 2, 4 and 6 months of age in Australia in 1999 and the coverage rate for the 3 primary doses of acellular pertussis vaccination at 12-months of age has been over 90% since 2001.<sup>1</sup> Nevertheless, hospitalisation rates of infants with pertussis remain high.<sup>2–4</sup>

Adolescent and adult household contacts are thought to be the most important source of pertussis transmission to infants.<sup>3–12</sup> Currently, adults aged over 20 years represent over 80% of notified pertussis cases in Australia.<sup>13</sup> Adolescents and adults with

pertussis may present with non-specific symptoms, making diagnosis difficult and delayed.

Acellular pertussis vaccines that are formulated for adolescents and adults are available and have been shown to be effective.<sup>14</sup> A publicly-funded booster pertussis vaccination program for adolescents was introduced in Australia in 2003. Since that time, the pertussis notification rate amongst teenagers has fallen but the notification rate for pertussis among the older adult population continues to increase.<sup>2,4,13,15</sup>

In Australia, a booster dose of pertussis vaccine is recommended for adults who work with young children. It is also recommended for parents planning a pregnancy, or as soon as possible after delivery of a baby.<sup>16</sup> A universal pertussis vaccination program for adults is difficult to justify due to problems with accurate estimation of pertussis incidence and on cost effectiveness grounds.<sup>17,18</sup> However, parental vaccination at the birth of a child could be cost effective.<sup>19,20</sup>

We performed a retrospective case-series study of hospitalised infants at a tertiary paediatric hospital in Brisbane, Australia. The survey targeted infants aged less than 12 months who had a diagnosis of pertussis in the decade between 1997 and 2006. The main aim of the study was to review the exposure history, vaccination status, and the quality of discharge International Classification of Diseases (ICD) coding of admission episodes of infants hospitalised with pertussis and to explore implications for future prevention.

## Methods

We identified hospitalised infants who were aged less than 12 months and had a diagnosis of pertussis between January 1997 and December 2006 from 2 sources. First, cases were identified from the Royal Children's Hospital (RCH) inpatient database, using discharge ICD codes including whooping cough due to:

- *Bordetella pertussis* (ICD 9.033.0, ICD 10.A37.0);
- an unspecified organism (ICD 9.033.9, ICD 10.A37.9);
- *Bordetella parapertussis* (ICD 9.033.1, ICD 10.A37.1); or
- other *Bordetella* species (ICD 9.033.8, ICD 10.A37.8).

The last 2 codes were included to capture *B. pertussis* that may have been incorrectly coded. Second, *B. pertussis* positive results at RCH were identified from the AUSLAB (2000 to 2006) and the PARIS (1997 to 1999) laboratory databases used by Pathology Queensland.

Using the dataset containing infant pertussis cases identified through both sources, we assessed the completeness of each source compared to the complete dataset. The dataset of all infants diagnosed with pertussis during the period was cross-checked with cases notified to the Communicable Diseases Branch (CDB) of Queensland Health using 4 primary linkage fields: first name, last name, sex, and date of birth. If only three out of 4 primary fields matched, then 1 secondary field, either date of admission for hospitalised cases or postcode, was used to confirm the link.

For this study we reviewed the following information from medical records of hospitalised infants using a standard data collection form: name; medical record number; sex; date of birth; ethnicity; immunisation status; contact history; admission date and discharge date; admission outcome; and diagnostic methods. Disease severity was assessed by intensive care unit (ICU) admission, ventilation support, and mortality. The diagnosis of pertussis was defined by the case definitions of the National Notifiable Diseases Surveillance System (Box). Due to small numbers, 2-tailed Fisher's exact tests were used for comparative analysis and a p-value of less than 0.05 was considered statistically significant.

The study was approved by the Human Research and Ethics Committee of the Royal Children's Hospital and Health Services District, Brisbane.

## Results

### Study population

We identified 59 cases of hospitalised infants aged less than 12 months with a possible diagnosis of pertussis infection between 1997 and 2006. These cases were identified from inpatient database (22 cases) and positive *B. pertussis* results from a hospital laboratory database (2 cases), or both (35 cases). One case was not reviewed as the patient's medical chart could not be found. Among the 58 reviewed cases, 55 cases met criteria for inclusion in this study. The 3 excluded cases were coded as having 'whooping cough due to unspecified organism' (ICD 9.033.9), but had alternative laboratory-confirmed diagnoses, including 2 cases of respiratory syncytial virus (RSV) infections and 1 case of parainfluenza virus type 3 (PIV3) infection.

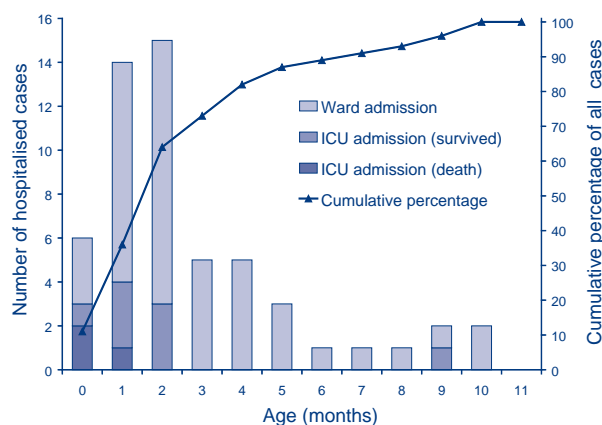
Of the 55 cases that met inclusion criteria, 45 were confirmed cases of whooping cough with detection of *B. pertussis* from laboratory tests. Seven were probable cases meeting only the clinical component of the case definition and had no other pathogen detected by laboratory testing.

The remaining 3 cases were diagnosed by their medical teams and the patients had symptoms including paroxysms of coughing or inspiratory whoop or post-tussive vomiting. However, at the time of discharge, the duration of the ongoing coughing illnesses in these cases had not reached 2 weeks. No further details about duration of cough post-discharge were available in the medical notes. No pathogens, including *B. pertussis*, were isolated by laboratory testing.

### Demography and seasonality

Thirty-five cases (64%) of hospitalised infants with pertussis were aged less than 3 months (Figure 1). Male infants accounted for 60% of all cases. According to admission records, 5 (9%) cases were identified as Aboriginal with four of these aged less than 2 months. All other cases were identified as non-Indigenous. Two peaks in the number of hospitalised infants with pertussis were seen (1997–1998 and 2001–2002), closely matching the epidemic pattern seen in overall disease notifications in Queensland over the review period (Figure 2).<sup>15</sup> There were 22 cases hospitalised between January 1997 and December 1998 and 14 cases hospitalised between January 2001 and December 2002. More cases (18/55, 33%) occurred in spring (September to November) than other seasons.

**Figure 1. Hospitalisation and outcome according to age for infants with pertussis, Royal Children's Hospital, Brisbane, 1997 to 2006**



## Box. Pertussis case definition

*Notifiable case definition of pertussis from January 2004:*<sup>4</sup>

### Reporting

Both **confirmed cases** and **probable cases** should be notified.

### Confirmed case

A confirmed case requires either:

- **Laboratory definitive evidence**
- OR
- **Laboratory suggestive evidence AND clinical evidence**
- OR
- **Clinical evidence AND epidemiological evidence**

### Laboratory definitive evidence

1. Isolation of *Bordetella pertussis*
- OR
2. Detection of *B. pertussis* by nucleic acid testing.

### Laboratory suggestive evidence

1. Seroconversion or significant increase in antibody level or fourfold or greater rise in titre to *B. pertussis* in the absence of recent pertussis vaccination)
- OR
2. Single high IgA titre to whole cells
- OR
3. Detection of *B. pertussis* antigen by immunofluorescence assay (IFA).

### Clinical evidence

1. A coughing illness lasting two or more weeks
- OR
2. Paroxysms of coughing OR inspiratory whoop OR post-tussive vomiting.

### Epidemiological evidence

An epidemiological link is established when there is:

1. Contact between two people involving a plausible mode of transmission at a time when:
  - a. one of them is likely to be infectious (from the catarrhal stage, approximately 1 week before, to 3 weeks after onset of cough)

AND

- b. the other has an illness which starts within 6 to 20 days after this contact

AND

2. At least one case in the chain of epidemiologically linked cases (which may involve many cases) is a confirmed case with at least laboratory suggestive evidence.

### Probable case

A probable case requires **clinical evidence** only.

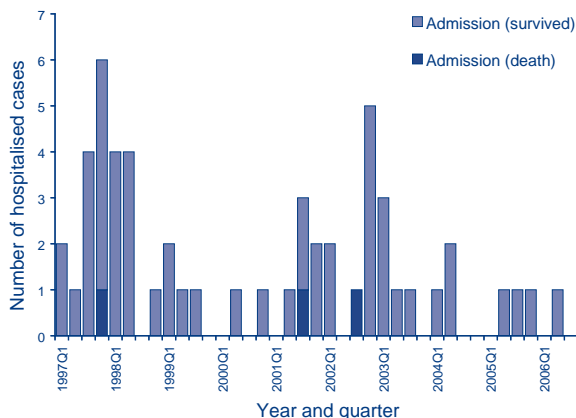
### Clinical evidence

1. A coughing illness lasting two or more weeks
- AND
2. Paroxysms of coughing OR inspiratory whoop OR post-tussive vomiting.

*Notifiable definition of pertussis in use prior to 2004:*<sup>21</sup>

- Isolation of *B. pertussis* from a clinical specimen
- or
- Elevated *B. pertussis*-specific IgA in serum or the detection of *B. pertussis* antigen in a nasopharyngeal specimen using immunofluorescence with a history of clinically compatible illness
- or
- An illness lasting 2 weeks or more with one of the following: paroxysms of coughing or inspiratory whoop without other apparent causes or post-tussive vomiting
- or
- an illness characterised by a cough lasting at least 2 weeks in a patient who is epidemiologically linked to a laboratory-confirmed case.

**Figure 2. Quarterly Royal Children's Hospital infant pertussis admissions, 1997 to 2006**



### Immunisation history

Documentation of immunisation status was available in all cases. Almost half (49%, 27/55) of all hospitalised infants had received no vaccine against *B. pertussis*, with 25 (93%) of these aged less than 3 months. In 29% (16/55) of hospitalised infants 1 dose of pertussis-containing vaccine had been received and 13% (7/55) had received 2 doses. Only 5 (9%) cases, all aged over 8 months, had completed a primary course of 3 doses of vaccine as required to protect against pertussis.<sup>16</sup>

Despite this, at the time of admission only 5 hospitalised infants (9%) were more than 2 weeks overdue for their most recent scheduled pertussis vaccination, with all of them between 3 months to 7 months of age: 1 case overdue for the 1st scheduled pertussis vaccine dose, one for the 2nd dose and two for the 3rd dose. One case had received no pertussis vaccine doses at 5 months of age.

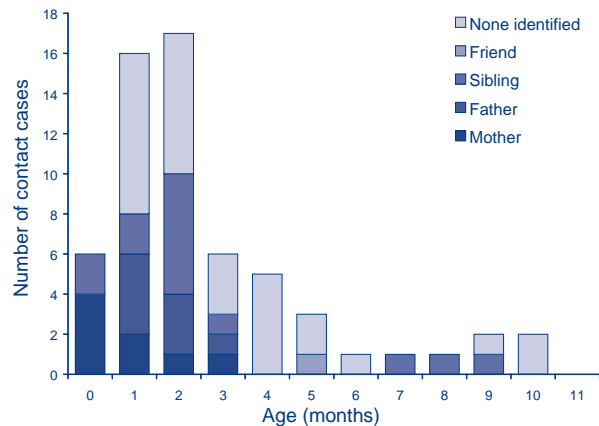
### Contact history

Of the 26 infants (47%) with at least 1 documented identifiable source of pertussis, 3 cases had 2 identifiable sources and 1 case had 3 identifiable sources (Figure 3). Of a total of 31 identifiable sources, 16 (52%) were parents and 11 of these parents reported a preceding prolonged cough illness. Of the hospitalised infants (13/15, 87%) where a parent was identified as a source the majority were aged less than 3 months.

Twenty-seven identified sources for 24 laboratory-confirmed infant pertussis cases, had symptoms compatible with pertussis. The remaining 4 identified sources for 2 clinically-diagnosed infant pertussis cases, had a cough illness lasting 2 weeks or more. Overall, 7 (23%) identifiable sources had

positive laboratory tests: *B. pertussis* IgA serology or polymerase chain reaction (PCR) on nasopharyngeal aspirate (NPA) and four of these were parents.

**Figure 3. Contact history of hospitalised cases of pertussis according to age of infants**



Cases that have more than 1 potential contact are represented multiple times in this figure.

### Admission duration and disease severity

The duration of admission ranged from two to 115 days, with a median duration of 6 days. When separated into age groups, infants aged less than 3 months had a longer admission with a median duration of 7 days versus 4 days for older infants.

Clinically, 51 cases (93%) had one or more of the following symptoms documented: paroxysms of coughing; respiratory whoop; or post-tussive vomiting. The other 4 cases did not have these symptoms, but had a cough illness lasting two or more weeks and had laboratory-confirmed *B. pertussis* infection. Overall, 30 cases (55%) had documented cough illness lasting two or more weeks.

Severe pertussis disease was more common in hospitalised infants aged less than 3 months (Figure 1). Of 35 hospitalised infants in this age group, 10 (29%) required ICU admission, and eight of these needed ventilation support, including all 3 deaths identified in this case series. In comparison, only 1 (5%) of the 20 hospitalised infants aged 3 months or older, required ICU admission ( $P=0.042$ ) and ventilation.

All 3 deaths in this case series were male infants aged less than 2 months and were laboratory confirmed with *B. pertussis* infection. Two of these cases were aged less than 1 month, had received no doses of pertussis vaccine, and had a parent identified as a source. The other case had received the 1st dose of

pertussis vaccine at 6 weeks of age—a week before presenting with clinical pertussis—and did not have an identified source.

A total of 9 hospitalised infants with pertussis (16%) had other concomitant infections. Of these cases, 5 cases were co-infected with another respiratory virus (2 cases of RSV, 2 cases of PIV1 and 1 case of PIV3). One case had co-infection with an adenovirus and cytomegalovirus. Other concomitant infections included 1 case of rotavirus gastroenteritis, 1 case of *Escherichia coli* urinary tract infection and 1 case with *Enterobacter cloacae* sepsis due to central venous line infection that developed after admission.

### Laboratory investigations

Tests on NPAs were the dominant laboratory diagnostic method used to detect *B. pertussis* in hospitalised infants. Between 1997 and 1999, 24 cases had a NPA immunofluorescence test for the detection of IgA antibody (IFA) performed and 15 cases (63%) were positive. From 2000 onwards, PCR replaced IFA as the standard laboratory test and 26 of 28 cases (93%) tested using this method, had positive results.

A total of 39 cases had NPA culture performed with 15 (38%) being positive. Seven of eight of these culture-positive cases also had positive NPA IFA and six of six cases had positive NPA PCR. A single culture-positive case only had culture performed, without IFA or PCR testing. Of the 24 culture-negative cases, six of 14 cases had positive NPA IFA and nine of 10 cases had NPA PCR positive. One culture-negative case had negative NPA IFA but positive IgA serology.

Overall, 34 cases had IgA serology tests performed with only 2 cases (6%) being positive. Both cases did not have other pathogens identified by laboratory testing. One case was a 1-month-old unvaccinated infant. The other case was a 10-month-old infant who had received the third dose of pertussis vaccine at 6 months of age. In this case the initial IgA serology on admission was negative, but the repeat test 10 days later, was positive.

During the period under review, the IgA serology test was decreasingly used as a method for diagnosis in hospitalised infants. Between 1997 and 1999, 21 of 26 cases (81%) had this test performed, compared with 13 of 29 cases (45%) between 2000 and 2007.

### Database completeness

Among the 55 cases that met inclusion criteria for this study, 53 cases (96%) were identified from the inpatient database through the discharge codes of

whooping cough and 37 cases (67%) were identified from positive *B. pertussis* results from the hospital laboratory database.

The reasons for the low sensitivity of laboratory database detection include tests performed at other laboratories (7 cases) and clinically-diagnosed cases with negative laboratory test results (10 cases). Only 1 case with a positive *B. pertussis* test result performed at the hospital laboratory did not appear on the computer generated search list from the hospital laboratory database. This was due to an unexplained error during the search process.

Incorrect discharge ICD coding of pertussis cases (9/55, 16%) was not uncommon. Eight cases with *B. pertussis* detected from various laboratory tests were incorrectly coded: four as 'whooping cough due to unspecified organisms'; one as 'whooping cough due to *B. parapertussis*'; one as 'whooping cough due to other *Bordetella* species'; and two as unrelated discharge codes. One case of whooping cough did not have an organism identified and was incorrectly coded as a case due to *B. pertussis*.

### Notifications to the Communicable Diseases Branch

Of the 55 hospitalised infant pertussis cases, 52 met the pertussis case definition in use at the time. Of 45 laboratory-confirmed cases of *B. pertussis*, 38 cases (84%) were notified to CDB; 36 of these were linked on 4 primary fields, and two linked on 3 primary fields and 1 secondary field. None of the 7 clinically-diagnosed pertussis cases were notified. Overall, only 73% of cases were notified.

Of the 7 laboratory-confirmed cases that were not notified, 6 cases occurred between 1997 and 1999 and they were recorded in the PARIS laboratory database. The other case that was not notified occurred in 2000 and was recorded in the current AUSLAB laboratory database.

### Discussion

Even in communities with high vaccination coverage, infants remain the most vulnerable to severe pertussis disease. In Australia, it has been suggested that many infants diagnosed with pertussis are overdue for immunisation time points.<sup>3,5</sup> However, on admission, less than 10% of infants in our case-series were more than 2 weeks overdue for their most recent scheduled pertussis vaccination. None of these were less than 3 months of age. An accelerated schedule of vaccination commenced at 6 weeks of age would not have prevented the deaths in our series, as all were aged under 2 months.

Options available to reduce the infant burden of pertussis include modifying the existing childhood schedule, or boosting immunity in parents and other infant contacts. A recent study in Germany showed neonatal immunisation with acellular pertussis vaccine given at birth, resulted in earlier antibody responses without inducing immunologic tolerance to pertussis antigens, but appeared to dampen response to a full primary course of *Haemophilus influenzae* type b vaccines at 7 months of age.<sup>22</sup> The second Global Pertussis Initiative meeting in 2005 recommended the implementation of a strategy involving immunising the household family members and close contacts of a newborn.<sup>20</sup> This 'cocoon strategy' may provide indirect benefit to protect infants against pertussis.

Our study suggests that parents remain the most important source of pertussis infection for infants. Educating and immunising parents planning a pregnancy, or who have recently had a baby may help to prevent pertussis infection in infants. Both of the two most recent editions of *The Australian Immunisation Handbook* have recommended this strategy.<sup>16,23</sup> Routine postpartum pertussis vaccination of women has recently been recommended by the Advisory Committee on Immunization Practices in the United States of America.<sup>24</sup> However, the uptake of the pertussis booster in parents is likely to be poor without a publicly funded program or more focused attempts to educate parents perinatally. Education campaigns will be required to increase clinician awareness and to target parents about pertussis infection.<sup>25</sup> Pertussis education at antenatal visits and in maternity units during the post-natal period may help to encourage the uptake of the pertussis booster in parents. Printed material could be included in the information pack parents receive in hospital, and pertussis vaccine could be offered to mother or both parents prior to discharge.

The period of our review saw a switch from whole cell to acellular pertussis vaccine and immunisation of adolescents with a booster dose added to the National Immunisation Program Schedule in Australia. Despite high vaccination coverage rates in infants since 2001, pertussis has remained endemic with epidemic cycles. Nearly two-thirds of hospitalised infants in our study were aged less than 3 months and had the greatest risk of ICU admission; the highest mortality; and were more likely to have a parent identified as the source of infection. Our findings confirm those of previous studies.<sup>5,12,26-29</sup>

Our study also shows the change in laboratory diagnostic methods from 1997 to 2006. For a variety of infectious diseases, PCR has been shown to be a more sensitive testing modality than traditional detection

methods, such as serology and culture.<sup>30</sup> Our findings are consistent with trends in age-specific pertussis diagnostic methods identified between 2000 and 2005.<sup>15</sup> A recent study showed positive NPA PCR results could be obtained up to 3 weeks following onset of catarrhal symptoms and up to 2 weeks following onset of paroxysmal cough.<sup>31</sup> NPA PCR will remain an important diagnostic tool for infant pertussis infection. By way of contrast, IgA serology tests for pertussis do not appear sensitive in infants, as they fail to develop measurable antibodies.<sup>32</sup>

With the broader ICD coding search criteria used in our study, we were able to identify 96% of infant pertussis cases from the inpatient database. However, nearly one in 6 cases had incorrect coding. Some of this misclassification may be explained by the unavailability of final laboratory results at the time of coding. However, the hospital discharge ICD codes of whooping cough are still considered reasonably reliable to monitor trends in infant pertussis.<sup>33</sup>

Over one-quarter of infant pertussis cases (27%) identified were not notified to the CDB; a finding similar to that of a previous New South Wales study.<sup>33</sup> All 7 laboratory-confirmed cases that were not notified occurred prior to 2001. Complete notification of laboratory-confirmed cases from 2001 is likely to be due to streamlined laboratory reporting processes incorporating automatic electronic notification of laboratory-confirmed results from the AUSLAB system. None of the 7 clinically-diagnosed cases were notified, despite this being required under Queensland legislation. A low notification rate of clinically-diagnosed pertussis cases was reported in a previous study in New South Wales.<sup>33</sup> Efforts to improve clinical notification of pertussis in infants are required, particularly in hospital settings where follow-up and chemoprophylaxis of vulnerable contacts are likely to be needed.

As with all observational studies, limitations must be considered before interpreting results. In this study these include the study's retrospective nature, a lack of detailed contact history and inclusion of 3 clinically-diagnosed cases that did not meet the diagnostic criteria for pertussis at the time of discharge. Not all identifiable sources had laboratory tests (23%), meaning some of the clinically-diagnosed sources may have been caused by other organisms producing a pertussis-like illness.

Pertussis remains a serious threat to Australian infants, particularly the very young, and parents continue to be an primary source of infection. More effort should be made to improve the public awareness of pertussis, particularly among parents who should also be targeted for vaccination in the perinatal period.

## Acknowledgements

The authors would like to thank Mr Bruce Imhoff from the Communicable Diseases Branch Information Systems for his assistance in gaining access to notification data and data linkage.

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