Finding the 'who' in whooping cough: vaccinated siblings are important pertussis sources in infants 6 months of age and under

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Abstract

Objectives: To describe the epidemiology of pertussis, and to identify changes in the source of pertussis in infants 6 months of age and under, during the 2008–2012 epidemic in south metropolitan Perth.

Design and setting: Analysis of all pertussis cases notified to the South Metropolitan Population Health Unit and recorded on the Western Australian Notifiable Infectious Disease Database over the study period. Information on the source of pertussis was obtained from enhanced surveillance data.

Results: Notification rates were highest in the 5–9 years age group, followed by the 0–4 years and 10–14 years age groups. There was a significant increase in the proportion of known sources who were siblings from the early epidemic period of 2008–2010, compared with the peak epidemic period of 2011–2012 (14.3% versus 51.4%, $p = 0.002$). The majority of sibling sources were fully vaccinated children aged 2 and 3 years.

Conclusions: The incidence of pertussis was highest in children aged 12 years and under in this epidemic. At its peak, siblings were the most important sources of pertussis in infants 6 months and younger, particularly fully vaccinated children aged 2 and 3 years. Waning immunity before the booster at 4 years may leave this age group susceptible to infection. Even if cocooning programs could achieve full vaccination coverage of parents and ensure all siblings were fully vaccinated according to national schedules, waning immunity in siblings could provide a means for ongoing transmission to infants. Recent evidence suggests that maternal antenatal vaccination would significantly reduce the risk of pertussis in infants 3 months of age and under. *Commun Dis Intell* 2014;38(3):E195–E200.

Keywords: pertussis, whooping cough, infants, source, vaccination, immunisation

Introduction

The incidence of pertussis (whooping cough) has risen both in Australia and internationally over recent years, and large epidemics have occurred.[1,2] Increased clinician awareness and laboratory testing are likely to be partially responsible for the apparent increase in disease incidence.[3] However, the epidemiology of pertussis in Australia and the United States of America has also changed in recent times, with an increasing proportion of disease occurring in children.[4–7] Possible reasons for this include the increasing use of less effective acellular vaccines[8–10] and increasing circulation of *Bordetella pertussis* strains deficient of vaccine antigen.[11,12] Within vaccinated populations, the fewer whole cell vaccines received, the greater the risk of pertussis.[8,10] Additionally, immunity from acellular pertussis vaccination wanes more rapidly than that from whole cell vaccination.[13–15] Pertussis morbidity and mortality are greatest in infants under the age of 6 months, who are too young to have completed a primary vaccination course. The implications of these changes for the source of infant pertussis remain unclear.

Household contacts are the most likely sources of infant pertussis, but there is variation in the proportion of sources reported to be parents as opposed to siblings. A recently published Australian review on infant pertussis sources reported the source as a parent in 55% (range 39%–57%) and a sibling in 16%–43%.[16] The proportion of sources that were siblings varied widely between studies, in comparison to the proportion that were parents, which were more consistent. The conclusion was that siblings may be more important sources of infant pertussis than previously realised.[16]

A prolonged outbreak of pertussis occurred in Australia, including south metropolitan Perth, between 2008 and 2012. A cocooning strategy involving the vaccination of caregivers of newborns was implemented in Western Australia and ran for 2011 and 2012 in attempts to protect newborns during the outbreak. This strategy can only be effective if caregivers are the main source of pertussis in infants.

Over the study period, the South Metropolitan Population Health Unit (SMPHU) collected enhanced surveillance data for pertussis cases in

children under 5 years of age. These data are not collected or reported at the national level so provide valuable additional information, particularly regarding source of infection, to that routinely collected for the National Notifiable Diseases Surveillance System. This study aimed to describe the epidemiology of the epidemic in south metropolitan Perth in relation to the source of infant pertussis, as well as any changes in the epidemiology and the source that occurred over the 5-year period.

Methods

The SMPHU is responsible for the follow up of notifiable diseases for the area covered by the South Metropolitan Health Service, which spans all of metropolitan Perth south of the Swan River and services approximately 37% of the Western Australian population.[17] Over the study period, the SMPHU collected enhanced surveillance data for pertussis cases in children under 5 years of age. The process involves a trained public health nurse interviewing the treating doctor and caregiver of the notified case, in order to obtain further information such as the likely source of infection and any high risk contacts. Enhanced surveillance defines a source of pertussis as a contact of the notified case who had either prolonged coughing illness or known pertussis infection, who was in contact with the notified case during the latter's incubation period (from 6 to 21 days prior to symptom onset). In the case of multiple possible sources, the source was assumed to be the individual who first became symptomatic, provided that the source's infectious period coincided with the notified case's incubation period.

Enhanced surveillance data for notified cases in infants 6 months of age and under were examined retrospectively, as well as pertussis notification data recorded on the Western Australian Notifiable Infectious Disease Database (WANIDD) for all age groups. All confirmed and probable cases meeting the case definition for pertussis were included if the optimal date of onset of pertussis occurred any time from 1 January 2008 to 31 December 2012, and residential postcode was within the SMPHU catchment area. The optimal date of onset refers to the earliest date recorded on WANIDD reflecting disease onset. In some situations, such as those where the caregiver of the notified case could not be contacted by telephone, enhanced surveillance data were not available. Notified cases and sources were defined as being fully vaccinated for age if on the optimal date of onset of illness they had received all pertussis vaccinations recommended by the Western Australian immunisation schedule for their age. This would potentially include vaccinations given within the 14 days preceding disease onset. The dates of vaccination for the source were not available so any such cases would be misclassified as being fully vaccinated for age at disease onset. Notified cases from the 2008–2010 and 2011–2012 periods were compared because this distinction allowed comparison of the pre-cocooning period with the cocooning period, and the early epidemic period with the peak epidemic period. Differences in age specific risk of infection as well as source of infant pertussis in the 2 periods were assessed.

Denominator data for notification rates were obtained from the Epidemiology Branch of the WA Department of Health. All analyses were performed in SPSS version 21. All comparisons were performed using chi-squared analyses or Fisher's exact test for categorical variables, and Mann-Whitney U testing for continuous variables. The study was approved by the Curtin University Human Research Ethics Committee (protocol approval SPH-16-2013). Ethics approval was not sought elsewhere, as this study formed part of the core business of the SMPHU.

Results

There were 3,611 cases of pertussis notified to the SMPHU from 2008 to 2012, with this period demonstrating a dramatic increase in notifications in comparison with previous years (Figure 1). Of these cases, 37.3% (n = 1348) occurred in children 12 years of age or under. At the peak of the epidemic in the December 2011 quarter, notification rates were markedly higher in children in age categories 14 years of age and under in comparison with the remainder of the population (Figure 1, Figure 2). The notification rate for the 5–9 years age group in the December 2011 quarter was 341.4 per 100,000, and 243.0 per 100,000 for the 10–14 years age group. Notification rates peaked in adults in this quarter also, but the amplitude of the peak was much less marked (56.0 per 100,000). Notification rates in children 4 years of age and under did not peak until the following quarter, at 206.8 per 100,000.

Of the 115 cases of pertussis in infants 6 months of age and under, enhanced surveillance data were available for 106 (92.2%). The optimal date of onset was the date of symptom onset for 111 of 115 cases, and the laboratory specimen date for the remaining four. There were no significant differences between those who had undergone enhanced surveillance and those who had not, comparing gender ($p = 0.74$), age ($p = 0.56$), ethnicity ($p = 1.00$) and hospitalisation status ($p = 0.48$).

The source was identified in 65 of 106 cases (61.3%). Two potential sources were identified for two of these cases, and one for the remaining 104 cases.

Figure 1: Notification rates of pertussis, south metropolitan Perth, 2008 to 2012, by quarter and age group

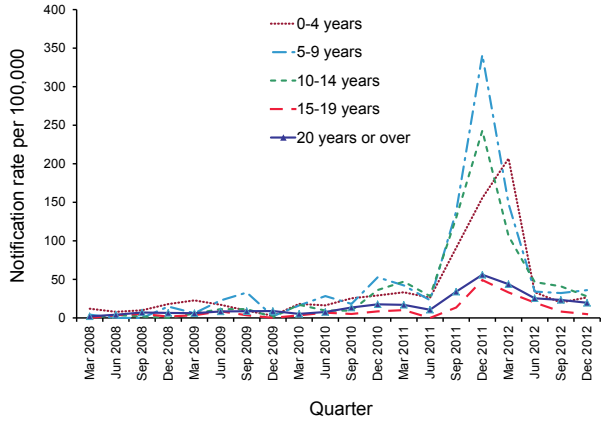
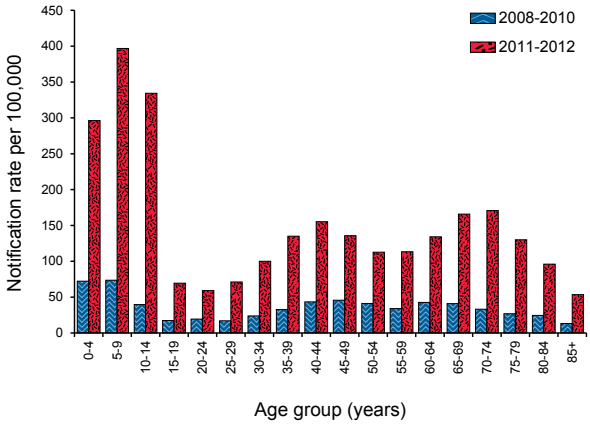


Figure 2: Notification rate of pertussis, south metropolitan Perth, 2008 to 2010 compared with 2011 to 2012, by age group



The proportion of sources whose diagnosis was confirmed with laboratory testing was unknown. Over the 5-year period, the source was a parent in 38.5% (n = 25) of cases and a sibling in 35.4% (n = 23) of cases. The most likely source of pertussis differed in the 2008–2010 period compared with the 2011–2012 period (Table). The proportion of parents as a source was lower in the 2011–2012 period (32.4%, n = 12 versus 46.4%, n = 13). However this difference was not statistically significant (p = 0.25). In contrast, the proportion of sources that were siblings was significantly higher in the 2011–2012 period (51.4%, n = 19 versus 14.3%, n = 4; p = 0.002).

During the 2011–2012 peak epidemic period, the ages of 14 of 19 sibling sources were known. Eight of these sources were aged from 2 to 4 years with five being fully vaccinated, one partially vaccinated, one unvaccinated, and one of unknown vaccination status. The true number of children in the 2–4 years age group may have been higher as the ages of 5 children were not recorded. Three sources were aged 6–11 years, and three were aged 12–19 years. Of all children in south metropolitan Perth diagnosed with pertussis in 2008–2012 and aged from 7 months to 4 years, 78.1% (n = 267) were fully vaccinated for age.

Discussion

Recent studies have shown an increasing incidence of pertussis in children but the implications of this for the source of infant pertussis have not been fully described. Identifying the source of pertussis in infants 6 months of age and under is crucial for the development of effective preventive strategies in this age group. However, the most likely source of infection will reflect local epidemiology, and if

Table: Source of pertussis in infants 6 months of age and under, south metropolitan Perth, 2008 to 2010 compared with 2011 to 2012

	2008-2010			2011-2012			Total		
	n	Known source %	Notified cases %	n	Known source %	Notified cases %	n	Known source %	Notified cases %
Parent	13	46.4	24.5	12	32.4	19.4	25	38.5	21.7
Sibling	4	14.3	7.5	19	51.4	30.6	23	35.4	20
Other household contact	3	10.7	5.7	2	5.4	3.2	5	7.6	4.3
Grand parent	3	10.7	5.7	3	8.1	4.8	6	9.2	5.2
Cousin	3	10.7	5.7	0	0	0	3	4.6	2.6
Other household contact	2	7.1	3.8	1	2.7	1.6	3	4.6	2.6
Total known source	28			37			65		
Notified cases with available enhanced surveillance data	45			61			106		
Notified cases 6 months of age and under	53			62			115		

the age specific risk of infection changes during epidemics, the source of pertussis in infants could vary at different points in the epidemic cycle. This study demonstrates changes in the source of infant pertussis corresponding with changing age specific risk of infection during an epidemic period.

Notification rates were highest in children in this epidemic, particularly at its peak in the 2011–2012 period. This correlated with a dramatic rise in the proportion of sibling sources. There are several possible explanations for the high notification rates in children. Recent studies suggest that acellular pertussis vaccine immunity wanes more rapidly than that of the whole cell pertussis vaccine.[8,10,13–15] The vaccine effectiveness of the whole cell pertussis vaccine previously administered in Australia was estimated at 91% (95% CI 85.5%–94.4%) in infants aged 8–23 months, and 84.5% (95% CI 78.3%–88.9%) in the 2–4 years age group.[19] In contrast, a recent Australian study reported the vaccine effectiveness of acellular vaccine to be 83.5% (95% CI 79.1%–87.8%) in infants aged 6–11 months, falling to 70.7% (95% CI 64.5%–75.8%) in children aged 2 years, and 59.2% (95% CI 51.0%–66.0%) in children aged 3 years.[20] In the whole cell pertussis vaccine effectiveness study, children had received 5 doses of pertussis vaccine by age 5 (2, 4, 6, 18 months and 4 years). In contrast, the acellular pertussis vaccine effectiveness for the children aged 2 and 3 years was calculated for children receiving 3 doses of vaccine, reflecting the current pertussis vaccination schedule of 2, 4, 6 months and 4 years.[20]

The high notification rates in children and the higher percentage of sibling sources could also be epidemic specific features, given the timing of this study. This is feasible as studies of contact patterns have shown high levels of assortative mixing in children.[21] Age specific infection risk and infant pertussis source types may be different in the inter-epidemic period. This would be congruent with the findings of this study, given that proportions of sources that were parents and siblings in the 2008–2010 period were comparable with those reported in previous literature.[16] Even if high incidence of pertussis in children and high proportions of siblings as sources are purely epidemic specific features, there are still implications for infant pertussis control measures during epidemics.

Cocooning programs are challenging to implement and there is no definitive evidence that they are successful in reducing the incidence of infant pertussis.[22,23] Parents remain susceptible to pertussis for 14 days following immunisation, due to the time taken to mount an immune response.[24] The earlier parental immunisation is performed post-natally, the better protected infants will be, making hospital-based vaccination ideal. Barriers to this have been identified, including legal issues related to vaccinating fathers (who are not hospital patients), and the need to provide after-hours services.[25] In Western Australia in 2011, an estimated 60% of mothers and 41% of fathers of newborns had been administered government funded pertussis vaccine, although the timing of this vaccination post-natally is unknown (2012 data not available at the time of publication).[26] These rates were similar to coverage rates reported in Victoria for the duration of their state wide cocooning program, where it was found that of those eligible, 68% of mothers and 49% of fathers were vaccinated.[22] In metropolitan areas of Victoria, 6% of mothers and 10% of fathers were vaccinated in the maternity hospital, compared with 70% of mothers and 42% of fathers in rural areas, suggesting that (particularly in metropolitan areas) vaccination may not have been given early enough in the neonatal period.[22] In this study, although the proportion of sources that were parents was lower in the cocooning period (2011–2012) compared with the pre-cocooning period (2008–2010), this observation did not reach statistical significance. While this may be a real finding, there were insufficient numbers in this study to determine that. If the difference in the proportion of source cases that were parents in the 2 periods were real, cocooning may explain this reduction, but it is likely to be insufficient to explain the observed increase in the proportion of sibling sources.

The increasing proportion of sibling sources over time reflected the increasing proportion of pertussis notifications in children 12 years of age and under over the 2008–2012 epidemic. In the peak epidemic period, sibling sources of infection were most likely to be aged 2 or 3 years. This suggests that the impact of high notification rates was greatest in the youngest siblings, despite the greatest numbers of cases occurring in children aged 7–11 years. Possible reasons for this include that siblings tend to be close in age, and that younger children are generally less able to control respiratory secretions. The only other recent Australian study of infant pertussis sources had similar findings, demonstrating that siblings aged 3 and 4 years were particularly important sources of infant pertussis during the 2009 epidemic in New South Wales.[27] Dutch research published in 2010 speculated that the high proportion of infant pertussis sources that were siblings (41%) in their study may have been related to the introduction of acellular pertussis vaccine in the Netherlands, as well as prior use of a less effective whole cell vaccine.[24] In that study, the source was a sibling aged 1–4 years in 18% of cases (95% CI 12%–25%), a sibling aged 5–8 years in 15% of cases (95% CI 9%–21%), and a sibling aged 9–13 years in

8% of cases (95% CI 4%–13%). The vaccination schedule for that population involved vaccination at 2, 3, 4 and 11 months, with a booster at 4 years introduced 5 years prior to the commencement of the study. There is a possibility that with the introduction of acellular pertussis vaccine, the interval between primary vaccination and booster doses in both the Dutch and Australian populations is now too long, resulting in waning immunity before the booster at 4 years. Even if all household contacts of newborns (including siblings) could be routinely fully vaccinated, the issue of breakthrough disease prior to the booster at 4 years would leave a certain proportion of siblings as possible infant pertussis sources, limiting the effectiveness of cocooning.

Vaccination in the 3rd trimester of pregnancy is an alternative measure for prevention of infant pertussis, with the benefit of placental transfer of maternal IgG to the infant. The vaccine effectiveness of the maternal antenatal vaccination program in the United Kingdom was estimated at 91% (84%–95% CI) for infants aged 3 months or less.[28] Following the introduction of the program, significant reductions in infant pertussis mortality, numbers of confirmed cases and numbers of hospitalisations were reported.[28] Adverse event surveillance has not detected any significant complications of maternal vaccination to date,[29] but further investigation is required into the possibility of infant immune response blunting.[28] Neonatal vaccination is an alternative possible means of infant pertussis control but similar concerns exist regarding immune blunting, requiring further study.[30] More research is also required to determine whether these observed antibody responses translate into lower incidence of pertussis in infants.

This study is a retrospective review of the data collected as part of the routine surveillance of pertussis, meaning there are several limitations. The source of pertussis was unable to be identified in 38.7% (n = 41) of cases who underwent enhanced surveillance. Previously published Australian studies on the source of infant pertussis have been unable to identify a source in 31%[27] and 49%[31] respectively. This could be due to the source being an asymptomatic or mildly unwell household contact, or a contact from outside the household unknown to the notified case or caregiver undergoing interview. If previously vaccinated adults are more likely to experience mild or asymptomatic illness, the proportion of infant pertussis sources that were parents could be underestimated in studies relying on the recall of the notified case and epidemiologic linkage rather than laboratory testing. However, siblings were the most common source of infant pertussis in a recently published study, which performed laboratory testing on all household contacts in order to identify the source.[24]

Another reason for the higher proportion of siblings noted in the 2011–2012 period could be that as the epidemic progressed, clinician awareness of pertussis in younger children increased, with a concurrent increase in laboratory testing. If this were the case, previous reports of sibling sources of infant pertussis may have underestimated the true proportion of sources attributable to siblings. Regardless, there are still implications for infant pertussis prevention and control measures.

This study has shown that a rapid increase in notification rates in children at the peak of the 2008–2012 epidemic in south metropolitan Perth was accompanied by a significant increase in siblings as sources of pertussis in young infants. In the face of widespread vaccination with a less effective acellular pertussis vaccine, it seems likely that notification rates will remain high in children. Fully vaccinated siblings aged 2 and 3 years were the most important infant pertussis sources in the peak epidemic period of this study, suggesting that immunity may wane in this age group before the vaccine booster at 4 years . Even if it were possible to fully cocoon infants through a combination of parental vaccination and ensuring siblings were fully vaccinated, the possibility of transmission via breakthrough disease in siblings would persist. The risk of sibling transmission to infants would be significantly reduced through the addition of a pertussis vaccine booster at 18 months and maternal antenatal vaccination, for which evidence of effectiveness at preventing pertussis in infants 3 months of age or less is mounting.

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