

A FIELD STUDY OF HOUSEHOLD ATTACK RATES AND THE EFFECTIVENESS OF MACROLIDE ANTIBIOTICS IN REDUCING HOUSEHOLD TRANSMISSION OF PERTUSSIS

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Abstract

Bordetella pertussis (whooping cough) is an endemic, highly contagious bacterial respiratory infection, which is notifiable to Australian state and territory health departments. Between 2008 and 2011 there was a substantial outbreak in New South Wales with an initial increase in cases occurring in North Coast New South Wales from late 2007. During September and October 2011 the North Coast Public Health Unit conducted a household study of secondary attack rates to assess the effectiveness of pertussis vaccination as well as the timely use of antibiotics in preventing household transmission. At the time the study was commenced, notified cases included a large proportion of individuals with a documented history of vaccination against pertussis. We found lower attack rates amongst vaccinated compared with non-vaccinated subjects in all age groups, with the exception of the 5–11 years age group, who were also primarily responsible for the introduction of pertussis into the household. There was an increased risk of pertussis transmission from the household first primary case to contacts when antibiotic treatment was commenced later than 7 days after the onset of symptoms compared with within 7 days. This protective effect of timely antibiotic treatment in relation to transmission highlights the need to control for antibiotic treatment in field studies of pertussis. The benefits of timely diagnosis and use of antibiotics in preventing household transmission underscore the importance of early presentation and diagnosis of pertussis cases, particularly in households with susceptible occupants. *Commun Dis Intell* 2015;39(1):E27–E33.

Keywords: *Bordetella pertussis*, household transmission, secondary attack rates, antibiotics, waning immunity, vaccine failure

Introduction

Bordetella pertussis (whooping cough) is a highly contagious bacterial respiratory infection endemic in Australia and notifiable in each of the states and territories under the respective public health acts.¹ In New South Wales the average crude notification rate for pertussis during the years from 2004 to 2007 was

59 per 100,000 population. New South Wales experienced an outbreak of pertussis from 2008 to 2011 when the crude notification rate increased to 154 per 100,000. This state-wide outbreak was initially apparent in the northern New South Wales region covered by the North Coast Area Health Service (NCAHS) and also in Western Sydney.² Within the NCAHS, the crude notification rates increased from 28 per 100,000 in 2007 to 206 per 100,000 in 2011. At the same time, the proportion of notified cases followed up by the public health unit with a documented history of complete pertussis vaccination increased from 29% of cases in 2007 to 82% in the outbreak years of 2011–2012. During this time there was increased media coverage of the outbreak and also a substantial increase in the use of polymerase chain reaction (PCR) as a method of diagnosis.² In response to the increasing number of pertussis cases who were not fully vaccinated the NCPHU conducted a study during late 2011 to investigate the household secondary attack rates of pertussis as well as the importance of timeliness in the use of macrolide antibiotic treatment in reducing household transmission.

Methods

Following ethical approval by the North Coast Area Health Service Human Research Ethic Committee, the NCPHU recruited households within the North Coast Area of New South Wales via routine follow up of laboratory notified cases during September and October 2011. Data were collected for all household members by telephone at the initial contact, and a follow-up interview took place within 28 days after the illness onset of the 1st case in the household.

Household members were classified according to the onset date of their illness. The first primary case (FP) was the person with the earliest onset date in the household. Household contacts whose onset of symptoms was within 7 days of the FP case were classified as co-primary (CP) cases. Those with symptom onset from 7 to 28 days of the FP or CP case in the household were classified as secondary (SEC) cases. Second primary (SP) cases were those individuals whose symptoms developed

28 days after any previously identified case in the household during the study period. Those individuals who remained symptom free during the study period were classified as non-cases. Cases were identified by the following methods:

- notified to the NCPHU by the laboratory following either a positive PCR or serology test;
- clinically diagnosed by the treating doctor;
- identified at household follow up with a clinical diagnosis using the New South Wales Department of Health pertussis response protocol for Public Health Units.³

The vaccination status of all children in the study was checked against the Australian Childhood Immunisation Register.⁴ Adults and children over 11 years were asked about history of receiving the adolescent or adult formulated pertussis vaccine (dTpa) and confirmation of vaccination was obtained through either the school-based records held at the NCPHU or from the person's general practitioner.

Fully vaccinated individuals under 12 years of age were defined as subjects who had completed the 3 course primary vaccination schedule and any booster doses required according to age by the Australian immunisation schedule.⁵ We considered subjects aged 6 months and under as not vaccinated ($n=4$). Study subjects aged 12 years or over who had not received a dTpa vaccine in accordance with the Australian immunisation schedule between the ages of 10–17 years or as an adult as recommended between 50–65 years of age, or as parents or carers in contact with infants, were classified as not vaccinated regardless of their childhood vaccination history.¹ Recall was used to indicate the vaccination status of adults and children over the age of 11 years where immunisation records were not available ($n=6$).

The following households were excluded prior to analysis: households with CP cases (to avoid issues related to multiple sources of exposure to household contacts); 1 household with a PCR positive asymptomatic case; households where the immunisation status of some members was unknown; and households where some individuals had a history of receiving some but not all of the required vaccinations for their age (partial vaccination). In order to avoid potential confounding of our analysis by age, we stratified the data by age groups that reflected the number of pertussis vaccines required according to the Australian immunisation schedule.

To assess the protection of vaccination in preventing household transmission, we measured the secondary attack rate in vaccinated household contacts compared with non-vaccinated contacts following exposure to a FP case.

We estimated the relative risk (RR) of contracting pertussis among household contacts (all ages) of FP cases whose treatment with antibiotics was commenced within 7 days, compared with commencement of treatment later than 7 days, between 8–14 days, between 15–21 days and later than 21 days after onset of symptoms. Logistic regression was used to identify factors related to the risk of a household contact becoming infected with pertussis. All analysis was conducted using StataSE 9 statistical software.⁶

Results

During the 2 month study period (September and October 2011) the NCPHU received 242 pertussis notifications and completed the household follow-up for 142 (58%) of these cases. During this time, an additional 6 cases were diagnosed by a doctor on clinical grounds, bringing the total number of initial cases to 148. During the course of household follow up an additional 48 cases were identified. The final study population included 454 individuals residing in 111 households, of these 196 were classified as cases (FP, CP, SEC, SP) and 258 were non-cases.

We excluded the following cases and their household from the analysis (Figure) (19 excluded households and 89 excluded subjects):

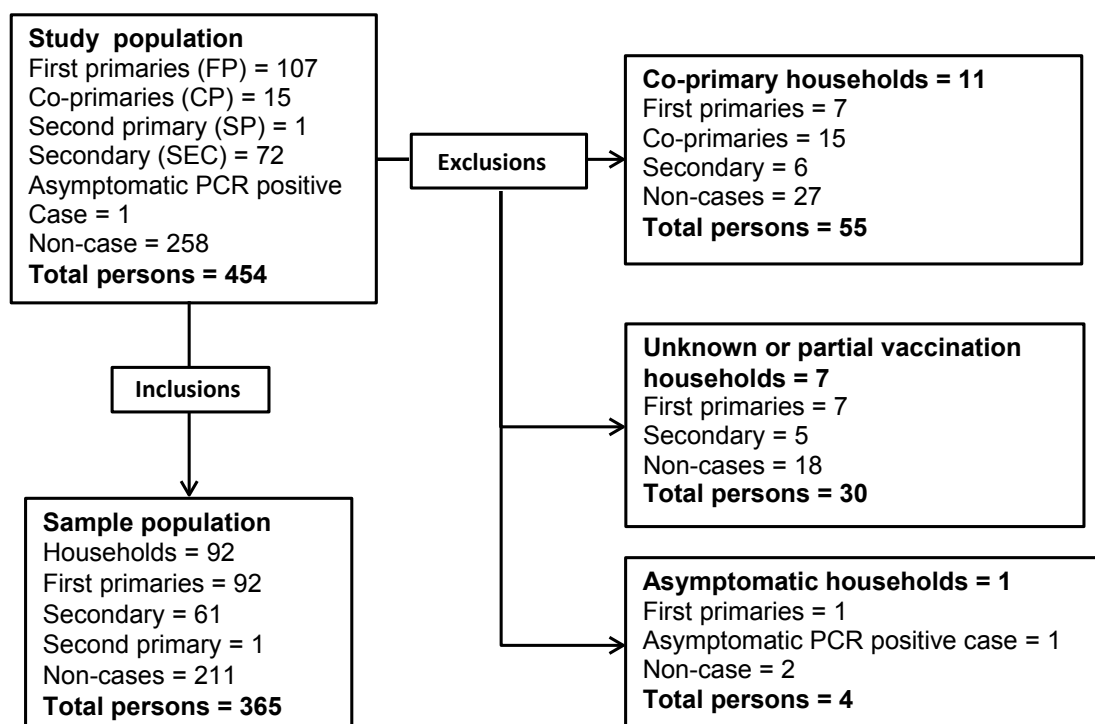
- 11 households of the 15 CP cases;
- 7 households where the vaccination status of a person was unknown or partial;
- 1 household where there was an asymptomatic PCR positive case.

Following these exclusions there were 92 households with 365 study subjects, which consisted of 92 FP, 61 SEC and 212 non-cases.

Description of study population

Table 1 summarises the study population by age group, case classification, and vaccination status. Overall, 52% of study subjects were vaccinated. There was no significant difference in the proportion of vaccinated non-cases (46%) compared with vaccinated SEC cases (54%), (difference = $-8%$, $P = 0.25$, 95% CI $-23%$ to $6%$). In comparison to the younger age group of 1–4 years (96% vaccinated), the 5–11 years age group (83% vaccinated) had a similar proportion of vaccinated subjects (difference = $-13%$, $P = 0.08$, 95% CI $-23%$ to $-3%$), but the proportion of vaccinated subjects decreased in the older age groups (12–19 years = 46%, difference = $-50%$, $P < 0.001$, 95% CI $-68%$ to $-33%$), (20+ years = 29%, difference = $-67%$, $P < 0.001$, 95% CI $-77%$ to $-57%$).

Figure: Summary of inclusions and exclusions for study subjects, North Coast household transmission study, 2011



The 20 years or over age group comprised 51% (186/365) of the total study subjects, 23% (21/92) of the FP cases, 38% (23/61) of SEC cases and 67% (142/212) non-cases. Compared with the 20 years or over age group, the 5–11 years age group comprised a smaller percentage of total study subjects at 30% (108/365), but they accounted for a significantly higher percentage of FP cases at 54% (50/92) ($P < 0.001$, 95% CI 44% to 65%) a similar percentage of SEC cases at 34% (21/61) ($P = 0.56$, 95% CI 23% to 46%) and a significantly smaller proportion of non-cases at 18% (37/212) ($P < 0.001$, 95% CI 12% to 22%). This indicated that the 5–11 years age group was predominantly responsible for introducing pertussis into the household.

Secondary attack rates

The secondary attack rate for all household contacts was 22.3%. The secondary attack rate for non-vaccinated household contacts was 19.6% compared with 25.4% for vaccinated contacts. However, the secondary attack rate was higher for non-vaccinated subjects compared with vaccinated subjects in all age groups, except for the 5–11 years age group where the attack rate was similar between vaccinated and non-vaccinated groups (Table 1).

Use of antibiotic treatment for pertussis

Thirty-four of the 92 FP cases commenced antibiotic treatment within 7 days of illness onset,

20 commenced treatment between 8–14 days of onset, 15 commenced treatment between 15–21 days of onset, 12 commenced treatment outside the recommended cut off of 21 days, 8 cases were not prescribed treatment and for the remaining 3 cases treatment was unknown. The 3 households where the FP treatment was unknown were excluded from the analysis of antibiotic treatment.

There was a statistically significantly higher proportion of vaccinated FP cases that received antibiotic treatment within 7 days compared with non-vaccinated FP cases (difference = 26% $P = 0.02$, 95% CI 6.2% to 44.8%). If the FP was vaccinated they were more than twice as likely to receive antibiotic treatment within 7 days of illness onset (RR = 2.17, $P = 0.02$, 95% CI 1.06 to 4.4). To ensure that the reduction in transmission of pertussis to household members was due to the antibiotic usage we compared the vaccination status of the contacts exposed to the FP who received timely antibiotic treatment. Within this cohort there was no difference in the proportion of vaccinated contacts compared with non-vaccinated contacts whose FP received macrolide treatment within 7 days of illness onset. ($P = 0.103$, 95% CI –2% to 22%). There was also no difference in the proportion of vaccinated contacts whose FP received macrolide treatment within 7 days compared with the proportion of vaccinated contacts whose FP had not received antibiotic treatment within 7 days of illness onset ($P = 0.10$, 95% CI –2% to 22%).

Table 1: Pertussis classification and vaccination status stratified by age, North Coast household transmissions study, 2011

Age (years)	Classification	Vaccination		Total number	SARv*	SARnv†
		Yes	No			
< 12 months	First primary	0	2	2	1	1
	Secondary	2	3	5		
	Non-case	0	0	0		
	Total	2	5	7		
1–4	First primary	10	0	10	0.56	1.00‡
	Secondary	9	1	10		
	Non-case	7	0	7		
	Total	26	1	27		
5–11	First primary	41	9	50	0.37	0.33
	Secondary	18	3	21		
	Non-case	31	6	37		
	Total	90	18	108		
12–19	First primary	0	9	9	0.06	0.09
	Secondary	1	1	2		
	Non-case	16	10	26		
	Total	17	20	37		
20+	First primary	7	14	21	0.07	0.17
	Secondary	3	20	23		
	Non-case	43	99	142		
	Total	53	133	186		
All ages	First primary	58	34	92		
	Secondary	33	28	61		
	Non-case	97	115	212		
	Total	188	177	365		

* SARv = Secondary attack rate for vaccinated.

† SARnv = Secondary attack rate for non-vaccinated.

‡ This estimated based on only 1 non-vaccinated subject.

The risk of illness was significantly increased for those contacts (all ages) exposed to a FP case whose treatment was delayed beyond 7 days compared with those exposed to a case treated within 7 days of their illness onset, RR = 3.89 (95% CI 2.00–7.55, $P < 0.001$). The risk of illness remained similar for those household contacts exposed to a FP case treated between 8–14 days and those whose FP case was treated between 15–21 days or over. Therefore in this study there was no reduction in household transmission when the FP case treatment was delayed beyond 7 days (Table 2).

Regression analysis

Logistic regression analysis investigated the odds of a contact being infected with pertussis or not. Univariate analysis found that the risk of a household contact becoming ill with pertussis was significantly associated with the household

FP case not being prescribed antibiotics within 7 days of the onset of illness (OR = 5.3, 95% CI 2.5–11.3, $P < 0.001$) (Table 3). We intended to build the model using household contacts becoming ill with pertussis (non-case/secondary case) as the outcome variable, and the following predictor variables: macrolide use, age, contacts immunised and FP immunised. However, the high correlation between a contact's age and contact's immunisation status ($r^2 = -0.49$, $P < 0.001$) meant it was not possible to include both these covariates in the same multivariate model.

From the multivariate analysis, the odds of a household contact getting pertussis was found not to be significantly associated with the FP immunisation status ($P = 0.12$), but was associated with FP antibiotic use and contact age. The odds of a contact getting pertussis was more than 6 times greater (OR = 6.7, 95% CI 2.9–15.4, $P < 0.001$) if

Table 2: Risk of pertussis for contacts exposed to a first primary case treated within 7 days of onset compared with longer time periods, North Coast household transmission study, 2011

Macrolide treatment	Classification		Relative risk	95% CI
	Secondary	Non-case		
Within 7 days	9	98	3.89	2.00–7.55 <i>P</i> <0.001
> 7 days	52	107		
Within 7 days	9	98	4.04	1.95–8.37 <i>P</i> <0.001
8–14 days	18	35		
Within 7 days	9	98	3.15	1.45–6.88 <i>P</i> =0.005
15–21 days	13	36		
Within 7 days	9	98	4.38	2.15–8.92 <i>P</i> <0.001
>21 days	21	36		

Table 3: Logistic regression models for odds of household contact getting pertussis

Model	Variable	OR	Std error	<i>P</i> value	95% CI
1	Macrolide*	5.29	2.048	<i>P</i> <0.001	2.48–11.3
2	Macrolide*	5.88	2.442	<i>P</i> <0.001	2.61–13.27
	Age†	5.66	1.957	<i>P</i> <0.001	2.88–11.15
3	Macrolide*	6.69	2.849	<i>P</i> <0.001	2.91–15.41
	Age†	5.55	1.928	<i>P</i> <0.001	2.81–10.96
	FP immunised‡	1.76	0.644	<i>P</i> =0.121	0.86–3.61

* Macrolide: 0 = contact first primary (FP) received antibiotic treatment within 7 days / contact FP did not receive antibiotic treatment within 7 days.

† Age: <12 year / 12+ years.

‡ FP immunised: yes or no.

the FP did not have antibiotic treatment (i.e. treatment commenced greater than 7 days after disease onset) compared with timely treatment (within 7 days of disease onset) with antibiotics, controlling for the contacts age and FP immunisation status. The odds of a household contact getting pertussis was more than 5 times greater (OR = 5.6, 95% CI 2.8–11.0, *P* < 0.001) for contacts aged less than 12 years compared with contacts aged 12 years or over, controlling for FP antibiotic use and FP immunisation status (Table 3).

Discussion

Within our study population we found that vaccination status decreased sharply by age from a high of 96% in the 1–4 years age group, to 83% in the 5–11 years age group, and 29% in the 20 years or over age group. The 5–11 years age group was predominately responsible for introducing pertussis into the household. The secondary attack rates for vaccinated and non-vaccinated subjects in the 5–11 years age group were similar, while for the 1–4 years and 20 years or over age groups the secondary attack rates were lower in the vaccinated

household contacts compared with those who were not vaccinated. These results suggest waning immunity in the 5–11 years age group and possibly a greater opportunity for exposure to pertussis at school. The vaccination rates coupled with the low secondary attack rates in adults may reflect past priming with whole cell vaccine,

We were unable to calculate vaccine efficacy due to the uneven distribution and low number of subjects across age groups, case classification and vaccination status.

The higher number of overall pertussis cases in the 5–11 years age group is consistent with a study by Fine et al (1988) who conducted a much larger household study of the protective effects of pertussis vaccine against household transmission. These authors found the pertussis vaccine provided a low protective effect to household contacts aged 5–12 years.⁷

Although Fine et al suggest this may be due to vaccine failure, more recent studies of the 2010 pertussis outbreak in California, United States of

America, identify an increase in disease incidence in this age group as being associated with waning immunity suggesting problems with durability of the acellular pertussis vaccine and the need to adjust vaccination schedules accordingly.^{8–10} Although post licensure field evaluations of vaccine effectiveness have been encouraged, such studies have various methodological difficulties that may underestimate or overestimate the benefit of the pertussis vaccine.^{1,7,11} Selection bias against such studies is introduced when they utilise laboratory reported cases to estimate secondary attack rates among household contacts, as our study has.⁷ It is generally accepted that vaccination within households is non-random and that risk factors for vaccine failure is intra familial in respect to deficiencies in the vaccine provider and genetics.⁷ Therefore, selection of immunised cases via routine pertussis reporting likely represents increased selection for vaccine failure of the entire household.

In our study, vaccine failure would likely have a disproportionate effect on estimates of secondary attack rates in the younger age groups due to these age groups having substantially higher proportions of vaccinated subjects compared with older age groups. Secondary attack rates would also be exacerbated by the problem of waning immunity in the 5–11 years age group, as there would already be a baseline proportion of the 5–11 years age group who are vaccine failures, therefore not developing immunity. Also, non-vaccinated cases that became infected with pertussis early in the outbreak would have developed natural immunity thus reducing the number of susceptible non-vaccinated people in the community later in the outbreak. Another issue is that our study was conducted late into a protracted 4-year long state wide pertussis outbreak and followed intensive media coverage. The percentage of vaccinated notified cases increased from 29% at the commencement of the outbreak period in 2008, to 82% at the time of the study in 2011. Possible reasons for the increase of notified vaccinated cases later in the outbreak may have been as a result of media attention on the outbreak leading to heightened concerns and increased reporting of pertussis by physicians and parents. Another possibility is there was an increase in testing due to the advent of the less invasive PCR test. All these issues could confound the estimation of secondary attack rates in our study.^{11,12}

Few studies have analysed timely antibiotic treatment of household FP cases and the subsequent effects on pertussis transmission rates. Previous work indicates that treatment of FP cases with antibiotics (erythromycin) has reduced infection rates.^{13–15} Within our study population, we found that treatment of FP cases with macrolide antibiotics or trimethoprim+sulfamethoxazol

substantially decreased pertussis transmission if commenced within 7 days of the onset of symptoms. This suggests medication use is an important potential confounder in studies of pertussis transmission and such studies need to control for medication use in the study design and analysis. We detected no difference in the proportions of non-vaccinated and vaccinated contacts of the FP case who received treatment within 7 days, indicating that the protective effect of timely treatment was not subject to bias by the vaccination status of the contacts. In addition to this, we found no statistically significant protective effects of vaccination against transmission from a FP case as there was no difference in the secondary attack rates from vaccinated FP cases compared with non-vaccinated FP case, suggesting the reduction in transmission from these cases was due to antibiotic treatment.

These results reinforce the benefit of prompt initiation of antibiotic treatment within 7 days of the onset of symptoms to reduce pertussis transmission to household contacts. Our analysis suggests that when the treatment of pertussis with antibiotics is delayed for longer than 7 days the amount of exposure to the transmission of pertussis from the FP case to contacts negates the reduction in transmission that the antibiotic treatment provides. It is important to emphasise that antibiotic treatment is still likely to be beneficial to the person infected with pertussis in reducing symptoms and severity, and our findings regarding prescription after 7 days are in relation to reducing transmission of the disease to contacts.

The results of our regression analysis reinforced our stratified analysis that the risk of household transmission of pertussis was related to timely antibiotic use and the contact's age. The risk of a contact getting pertussis was more than 6 times greater if the FP did not have timely antibiotic treatment (within 7 days) compared with those contacts whose FP case was commenced treatment within 7 days. The risk of contracting pertussis following exposure to FP case was more than 4 times greater for contacts aged less than 12 years compared with contacts aged 12 years or over.

Vaccination status was assessed using immunisation records except for 6 subjects where subject recall was used. Of those 6 individuals, one was a member of a household excluded due to the presence of a co-primary case and the remaining 5 individuals were distributed throughout the age strata, indicating minimal change in the secondary attack rates for the two affected age groups. While we acknowledge this may have introduced some recall bias we believe any impact on our study would be negligible.

The case definitions applied in our study were based on either laboratory evidence or clinical evidence and there may have been some misclassification in the application of clinical evidence. This may have resulted in different determinations of cases among vaccinated and non-vaccinated groups resulting in inaccurate attack rate estimates.^{8,13} Factors that may have resulted in case misclassification of individuals in our study include:

1. reliance on clinical history to determine case status and potential differences in reporting symptoms between immunised and non-immunised households; and
2. more likely reporting of a history of cough by parents of young children compared with older age groups resulting in a more sensitive case definition.

Our study found that children aged 5–11 years of age were the primary source of pertussis in the household and that timely antibiotic treatment of the primary household case substantially reduce pertussis household transmission. Interestingly, the use of antibiotic treatment is not generally documented in studies of household transmission estimating vaccine effectiveness and we recommend future studies assess this issue.¹³ The consequential confounding effects along with methodological problems associated with using notified cases and households as the study populations make field evaluation of pertussis vaccine difficult. It is unclear if our findings on increased risk of household transmissions among younger age groups may be due to higher susceptibility, more sensitive case diagnosis, waning immunity or other factors and further research is required to clarify these issues.

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