

# A Pertussis Outbreak among Daycare Children in Northern Israel: Who Gets Sick?

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**ABSTRACT:** **Background:** An outbreak of pertussis occurred in a daycare center with 87.5% vaccination coverage.

**Objectives:** To assess the effectiveness of the acellular pertussis vaccine and prevention of pertussis after chemoprophylaxis with azithromycin.

**Methods:** We studied 31 daycare children aged 3–5.5 years exposed to a child with pertussis. Nasopharyngeal swabs were obtained for *Bordetella pertussis* culture and polymerase chain reaction initially, and at days 21 and 60 of follow-up, in cases exhibiting symptoms.

**Results:** Of the 31 daycare children 6 (19%) tested positive for *B. pertussis* by PCR, 4 of whom had not been vaccinated against the disease. Of the two vaccinated children who contracted pertussis, one had milder symptoms and the other was asymptomatic. The incidence of pertussis was significantly lower in the vaccinated group (2/27) than in the unvaccinated group (4/4) ( $P=0.000$ ), with efficacy of the vaccine calculated to be 92.5%. Azithromycin chemoprophylaxis was taken only by 14 of the 25 exposed children (56%). On day 21 follow-up, there was no further laboratory-diagnosed *B. pertussis* cases in any of the exposed children, regardless of whether or not chemoprophylaxis was taken.

**Conclusions:** Based on the children's clinical manifestations and PCR findings a pertussis outbreak had occurred in the daycare center studied. Our findings support the importance of pertussis vaccination since all the unvaccinated children in the daycare center contracted the infection.

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**KEY WORDS:** *Bordetella pertussis*, polymerase chain reaction, outbreak

**A**lthough the incidence of pertussis has decreased following the introduction of the pertussis vaccine, over the last two decades there has been a resurgence of disease in many countries [1] with some of this resurgence occurring in outbreak settings [2]. Nevertheless, while there are controlled trials of acellular pertussis (DTaP) vaccine efficacy and prospective studies of

effectiveness [3], few studies have examined DTaP effectiveness in an outbreak setting, and even fewer have explored the efficacy of macrolide post-exposure prophylaxis in such settings. To address these issues the current study used data collected from individuals exposed to a pertussis outbreak (December 2005 to January 2006) in a daycare center, where a relatively high proportion of children were not immunized.

## SUBJECTS AND METHODS

This study was conducted in Israel where, despite vaccination at age 2, 4, 6 and 12 months, there has been an ongoing upward trend in the incidence of pertussis over the last 20 years [4–8]. The study participants were 31 of the 32 attendees and 3 staff members employed at a private, licensed daycare center. The age range was 3.5–5.0 years (mean  $4.2 \pm 0.8$  years) for the children and 26–48 years for the staff members. The daycare center is located in a single building with one large hall functioning as the common play area.

## PROCEDURE

The immunization status, reported by the parents as the number of vaccines administered, the demographics and the clinical data were collected via a written questionnaire completed by the parents on day 1. Also on day 1, two nasopharyngeal Dacron swab specimens (Medical Wire, Medeco, Corsham, UK) were collected for culture and PCR from the study participants. All laboratory testing was conducted at Bnai Zion Medical Center's clinical microbiology laboratory. Specimens were immediately plated on charcoal agar plates (Hylabs, Rehovot, Israel) and incubated at 37°C for 14 days. Polymerase chain reaction targeting IS481 and pertussis toxin primers was performed from the nasopharyngeal specimen using a semi-nested PCR (Proligo LLC, Boulder, CO, USA) [9,10]. The PCR test was considered positive only if both targets tested positive. The laboratory adhered to standard PCR precautions. When pertussis was diagnosed, children were advised to remain at home for 5 days of treatment with azithromycin (10 mg/kg on the first day followed by 5 mg/kg for the subsequent 4 days). Azithromycin was chosen because of its effectiveness and tolerability [11,12]. In addition, on day 1, all contacts of the exposed individuals were

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PCR = polymerase chain reaction

prescribed chemoprophylaxis with the same azithromycin regimen. Follow-up phone calls were conducted on days 21 and 60 to the parents of all 32 children. Moreover, for surveillance of additional cases, parents of initially asymptomatic children were questioned about the development of disease symptoms. Repeat nasopharyngeal specimens for PCR and culture were obtained for children with cough symptoms of at least 4 days duration.

With regard to case definition, Centers of Disease Control criteria were used to categorize cases as confirmed, suspected, or probable [13].

After determining the rate of pertussis in both unvaccinated (0 doses) and vaccinated children, the vaccine effectiveness was calculated. Vaccine effectiveness equals  $[(PRU - PRV) / PRU] \times 100$  [11].

## RESULTS

### VACCINE EFFECTIVENESS

Of the 32 daycare children 31 participated in the study. The non-participant was a 4 year old fully immunized child who had no cough symptoms during the study period and whose parents did not wish to be included in the study. Demographic and clinical features of the pertussis cases are summarized in Table 1 and Figure 1. Only 4 of the 31 children in the daycare center were unimmunized despite the fact that these children had no medical contraindication or precaution for pertussis immunization. No further explanations for vaccination refusal were given. The remaining 27 children had all received four doses of acellular pertussis vaccine (Infanrix<sup>®</sup>, SmithKline Beecham Biologicals). For the daycare children, the time from the last dose of pertussis vaccine to the current outbreak ranged from 2.5 to 4 years. None of the families reported previous illness with pertussis.

Among the 31 children, 6 (19%) fulfilled the case definition for pertussis in an outbreak setting. Four of these six (cases 1–4) were unimmunized and developed a prolonged

**Table 1.** Epidemiological, clinical and laboratory findings in pertussis patients

Case no.	Age (yrs)	Duration of cough <sup>§</sup>	No. of vaccine doses	PCR
1	5.5	4*+	0	Positive
2	5	4*	0	Positive
3	4.5	3*+	0	Positive
4	3	2*	0	Positive
5	3	1*+	4	Positive
6	4.5	3*+	4	Negative

<sup>§</sup>Duration of cough: 1 = one week, 2 = more than one and less than 2 weeks, 3 = more than 2 and less than 3 weeks, 4 = more than 3 and less than 4 weeks

\* Paroxysmal cough

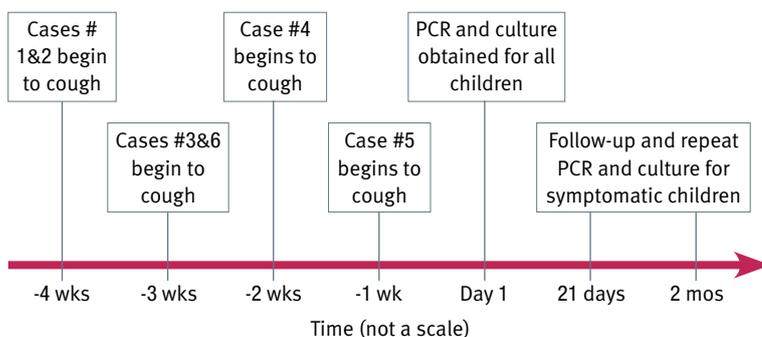
+ Whoop

paroxysmal cough lasting at least 1–2 weeks, thus fulfilling the CDC's confirmed case classification on day 1. The PCR tests for all four of these patients were positive, but their nasopharyngeal specimens were culture-negative. Although suspected on day 1, pertussis was confirmed in one of the vaccinated children solely on the basis of a positive PCR test (case 5). Regarding the other vaccinated child with suspected pertussis (case 6), the case was confirmed on the basis of clinical symptoms and the establishment of an epidemiologic link to another individual with a positive PCR. Overall, pertussis was less prevalent in the fully vaccinated group (2/27) compared with the non-vaccinated group (4/4). Unvaccinated children acquired their pertussis earlier than the vaccinated children [Table 1, Figure 1]. There were no positive pertussis cultures. All staff members denied cough and tested negative for pertussis (culture and PCR). The calculated effectiveness of the acellular pertussis vaccine was 92.5 (95% confidence interval 40–98).

### EFFICACY OF CHEMOPROPHYLAXIS

On day 1 all children in the daycare center were advised to take azithromycin as chemoprophylaxis according to the regimen noted in the Methods section. For those children with suspected pertussis on day 1, parents were informed that this same prescription was given as treatment rather than prevention. Household contacts of children with confirmed disease were advised to also begin chemoprophylaxis by day 3. Since all the unvaccinated children in the daycare center contracted pertussis and all the exposed children were fully immunized, no booster vaccine was recommended. Phone interviews, conducted with parents on days 21 (first follow-up) and 60 (second follow-up), were used to assess compliance to treatment and chemoprophylaxis.

**Figure 1.** Timeline of pertussis infection in the daycare center (case# from Table)



PRU = the rate of pertussis in unvaccinated children  
PRV = the rate of pertussis in vaccinated children

CDC = Centers for Disease Control

laxis and to identify additional suspected cases. Only 14 of the 25 exposed (vaccinated) children at the daycare center (56%) took the chemoprophylaxis. No adverse side effects were reported during follow-up. Regarding additional case identification, at the first follow-up, 5 of the 25 exposed but undiagnosed children had developed an upper respiratory tract infection with cough (3 of the 5 had completed prophylaxis whereas 2 had declined azithromycin,  $P = 0.62$ ). In all cases, the cough was neither paroxysmal nor accompanied by a whoop. Repeat testing for pertussis among those who developed upper respiratory tract infection was negative. By the second follow-up phone call, all exposed children were asymptomatic.

## DISCUSSION

The children's clinical manifestations and PCR findings clearly point to a pertussis outbreak in the daycare center. Our findings reaffirm the importance of pertussis vaccination since all the unvaccinated children in this center contracted the disease. The results reported here indicate that the DTaP vaccine applied in the context of a four-immunization regimen provides effective coverage for recently vaccinated children exposed to a pertussis outbreak. As noted above, the calculated effectiveness of the acellular pertussis vaccine was  $> 90\%$ . Furthermore, although the limited number of observations in our study precludes any firm conclusions, our data suggest that azithromycin-based chemoprophylaxis may offer a modest added benefit to recently vaccinated children exposed to a pertussis outbreak.

These findings are important because pertussis outbreaks are common and occur in all age groups and in a wide variety of settings, including hospitals, schools, daycare centers, army barracks, nursing homes, etc. [2,15,16]. For example, reports in recent years have documented outbreaks of pertussis in populations of largely unvaccinated children in Afghanistan [17].

Studies in the U.S., Europe and Africa have mainly focused on evaluating the general (as opposed to outbreak-specific) efficacy of different DTaP vaccines after three doses and have found efficacy to be 73–89% [18,19]. Efficacy levels for the whole-cell pertussis vaccine are more variable and tend to be lower than for the acellular vaccine [20], and estimates for both types of vaccines may be even more variable when tested under conditions of household exposure [21] or community-wide outbreak [22,23]. Thus, one possible explanation for the higher effectiveness rate in the current study is that vaccine effectiveness was calculated in the context of a single, community-wide outbreak. Alternatively, the higher rate may be associated with the additional protection afforded by the fourth vaccine dose and because all the children in the current study were only 2–4 years post-vac-

ination. The latter explanation is consistent with the results of Bisgard's recent study reviewing the high effectiveness of pertussis vaccine among recently vaccinated children [3]. In the epidemiologic investigation of this outbreak, specimens for both culture and PCR were obtained. Notably, the laboratory confirmation of pertussis in this daycare outbreak was PCR-based with no culture-positive specimens. Some comment on the laboratory findings is warranted: *B. pertussis* is a fastidious gram-negative coccobacillus, and its isolation from nasopharyngeal secretions is difficult. Given the relative complexity of proper collection with specific swabs and media, a negative culture does not exclude the diagnosis of pertussis. The yield of *B. pertussis*-positive culture depends in part on when the specimen is taken, since most growth occurs in specimens obtained in the early catarrhal stage of the disease. In this outbreak, for some of the children nasopharyngeal specimens were obtained as late as 4 weeks after the onset of coughing. Finally, it should be noted that the ratio of positive PCR samples to positive cultures ranges from 4 to 6:1, respectively [24].

Regarding the efficacy of azithromycin-based prophylaxis, whereas the current CDC recommendations advise chemoprophylaxis for all household and close contact exposures to pertussis, some countries like Canada and the UK recently narrowed their recommendations. For example, the South Yorkshire Health Protection Unit advises that chemoprophylaxis be administered to vulnerable contacts including neonates, unimmunized or partially immunized infants or children, an individual with a chronic illness, or an immunocompromised host [25]. In their 2005 Cochrane review, Altunaiji et al. [11] conclude that there is insufficient evidence to determine the exact benefit of prophylactic treatment of pertussis contacts. Our findings are consistent with such policy recommendations, namely, among those vaccinated there was no evidence of subsequent disease regardless of prophylaxis status. Specifically, although chemoprophylaxis was recommended for all exposed children, staff and family contacts of exposed children, only 14 of the 25 exposed but non-diagnosed children (all recently vaccinated) took the chemoprophylaxis, with no statistical difference regarding the development of subsequent disease between those children whose parents followed the chemoprophylaxis regimen and those who did not. Nevertheless, given the small number of cases in the population studied, our findings must be interpreted with a high degree of caution. Thus, while these findings may be viewed as further support for the UK's guidelines regarding chemoprophylaxis among fully immunized individuals, pending further research, it remains most prudent to adhere to the CDC-recommended pharmacologic control measures after exposure to pertussis, and particularly, after exposure in the context of an outbreak such as described here.

## CONCLUSIONS

The efficacy of the acellular vaccine was 92.5% among young children in a daycare center. While the study was not designed to assess the efficacy of azithromycin chemoprophylaxis in pertussis outbreaks, some possible conclusions can be drawn. The initiation of azithromycin did not afford any added benefit in preventing the development of pertussis among recently vaccinated children exposed to the disease in an outbreak setting, and despite the small number of subjects, this study raises questions about the added value of chemoprophylaxis in this age group.

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