

Unexpectedly Limited Durability of Immunity Following Acellular Pertussis Vaccination in Preadolescents in a North American Outbreak

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(See the Editorial Commentary by DeMaria Jr, on pages 1736–8.)

Background. Despite widespread childhood vaccination against *Bordetella pertussis*, disease remains prevalent. It has been suggested that acellular vaccine may be less effective than previously believed. During a large outbreak, we examined the incidence of pertussis and effectiveness of vaccination in a well-vaccinated, well-defined community.

Methods. Our center provides care to 135 000 patients, 40% of the population of Marin County, California. A total of 171 patients tested positive for *B. pertussis* from 1 March to 31 October 2010 by polymerase chain reaction (PCR). Electronic medical records were reviewed for demographic characteristics and vaccination status.

Results. We identified 171 cases of clinical pertussis, 132 of which were in pediatric patients. There was a notable increase in cases among patients aged 8–12 years. The rate of testing peaked among infants but remained relatively constant across ages until 12 years. The rate of positive tests was low for ages 0–6 years and increased among preadolescents, peaking among those aged 12 years. The vaccination rate among PCR-positive preadolescents were approximately equal to that of controls. The vaccine effectiveness was 41%, 24%, and 79% for children aged 2–7 years, 8–12 years, 13–18 years, respectively.

Conclusions. Our data suggests that the current schedule of acellular pertussis vaccine doses is insufficient to prevent outbreaks of pertussis. We noted a markedly increased rate of disease from ages 8–12 years, proportionate to the interval since the last scheduled vaccine. Stable rates of testing ruled out selection bias. The possibility of earlier or more numerous booster doses of acellular pertussis vaccine either as part of routine immunization or for outbreak control should be entertained.

Whole-cell pertussis vaccination has been shown to be highly effective at reducing rates of pertussis in young children [1]. The acellular pertussis vaccines were introduced in the United States in 1991. Although comparably efficacious, adverse reactions from acellular pertussis vaccination are markedly reduced, when contrasted with whole-cell vaccine [2]. For this reason, the acellular vaccine is now the sole pertussis vaccine

used in the United States, despite its higher cost. Efficacy for the acellular pertussis vaccine has been between 84% and 85% for children and 92% for adolescents and adults [2, 3]. More recently, there have been suggestions that the efficacy of the acellular vaccine may not be as robust as reported in these initial studies [4–6]. These vaccines have not been extensively studied for clinical efficacy in North America, and no studies exist for long-term immunogenicity. Additionally, it is well-known that immunity in response to natural infection is limited in duration and persists for 4–20 years [7]. Despite this lack of data on the durability of acellular pertussis vaccine, recommendations were made by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) to follow the existing schedule for the more effective

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whole-cell vaccine (ie, ages 2, 4, 6, and 15–18 months and 4–6 years) [8,9].

In 2006, the ACIP broadened the recommendation to include vaccination of adolescents for pertussis. This was enabled by the 2005 licensure of acellular pertussis vaccines (ie, vaccines containing tetanus and diphtheria toxoids and acellular pertussis [Tdap]) for adolescents and adults. The new guidelines recommend a Tdap booster at the age of 10–12 years to address the limited durability of pertussis vaccine. A 1-time booster for adults was recommended to address the persistent reservoir in adolescents and adults [10,11].

During 2010, California experienced the largest epidemic of pertussis in 53 years. Statewide, the incidence was 20 cases per 100 000 people [12]. This is the highest rate in California since 1958, when there was an incidence of 26 cases per 100 000 [12]. Marin County had the second highest incidence in the state, with 136.48 cases per 100 000 people [12]. San Rafael Kaiser Permanente Medical Center was at the epicenter of this epidemic. In reviewing cases confirmed at our medical center during this outbreak, we noted effective protection of younger children. Our unvaccinated and undervaccinated population did not appear to contribute significantly to the increased rate of clinical pertussis. Surprisingly, the highest incidence of disease was among previously vaccinated children aged 8–12 years. We sought to examine the factors that resulted in this peak.

METHODS

Approval for the study was obtained from the Institutional Review Board of the Kaiser Foundation Research Institute (Oakland, CA). Kaiser Permanente Medical Center in San Rafael, California, is the primary source of care for 135 000 people, the majority of whom reside in Marin County. This medical center consists of a core hospital with 120 inpatient beds and 6 associated clinics. Approximately 40% of the total population of 252 409 in Marin County receives their care solely at this medical center [13,14]. Kaiser Permanente is an integrated healthcare system, with its own laboratories, hospitals, and clinics, and uses an electronic medical record. This structure permits review of all laboratory results, hospitalizations, and outpatient visits in Northern California.

Nasopharyngeal specimens for pertussis testing were obtained using a BD BBL Cultureswab with liquid Stuart media (BD catalog no. 220133; Becton, Dickinson and Company, Franklin Lakes, NJ). Laboratory testing is centralized. Real-time polymerase chain reaction (PCR; Cepheid Corporation, Sunnyvale, CA) analysis is the basis of all pertussis testing, with required concomitant testing for both *Bordetella pertussis* and *Bordetella parapertussis* performed using the Cepheid GeneXpert platform, which amplifies IS481 or IS1001 for detection of *B. pertussis* or *B. parapertussis*, respectively.

All patient data were retrieved from the electronic medical record, including those for case patients and the population as a whole. At the start of the epidemic, the Department of Pediatrics made a practice agreement that any patient between 0 and 18 years of age with ≥ 1 week of unexplained cough-associated illness would undergo PCR analysis for pertussis. Any intimate contact of a person with known pertussis and cough symptoms would also be tested for pertussis. The department is a part of an integrated health system, and clinical guidelines and practice advisories are generally followed in a rigorous manner. No additional epidemiologic information was recorded.

All positive PCR results for *B. pertussis* from this medical center between 1 March and 31 October 2010 were identified, and patient records were reviewed for age, vaccination status, vaccination refusal, and date of most recent vaccination before clinical pertussis presentation. Vaccination status was categorized using the CDC vaccination guidelines [8–10]. Patients who had completed the full number of CDC-recommended vaccine doses for their age at the time of clinical presentation were identified as being current with the vaccination schedule. If a patient had record of past vaccinations but received fewer than the recommended number, the patient was identified as under-vaccinated. If a patient had no record of past vaccinations, their charts were reviewed further to determine whether vaccination was received elsewhere or whether a personal belief exemption or permanent medical exclusion was identified.

The manufacturers of vaccines administered prior to 2002 could not be retrieved. Vaccines used since 2002 included Infanrix, Pediarix, and Boostrix (GlaxoSmithKline, Research Triangle Park, NC) and Daptacel, Pentacel, and Adacel (Sanofi Pasteur, Bridgewater, NJ).

Data were entered into an Excel 2007 data sheet for processing (Microsoft, Redmond, WA). Information was then anonymized.

Statistical analysis was completed using R (R Foundation for Statistical Computing, Vienna, Austria) with the accessory packages Deducer (Ian Fellows) and Java Gui for R (Markus Helbig, Simon Urbanek, and Ian Fellows).

Vaccine effectiveness was calculated using the screening method [15], as follows:

$$VE = 1 - \frac{PCV}{1 - PCV} \times \frac{1 - PPV}{PPV},$$

where PCV is defined as the proportion of cases vaccinated, PPV is defined as the proportion of population vaccinated, and VE is defined as vaccine effectiveness. For the purposes of this calculation, cases were divided into ages 2–7 years, 8–12 years, 13–18 years, and 2–18 years. Cases aged <2 years were excluded, as they would not have completed the recommended vaccination course. We defined the age groups to permit

Table 1. Attack Rates Among Vaccinated Patients and Among Undervaccinated and Unvaccinated Patients

Age Group (Years)	Attack Rate, Cases/100 000 Person-Years		<i>P</i> ^a
	Vaccinated Persons	Undervaccinated and Unvaccinated Persons	
2–7	359	606	.57
8–12	2453	3211	.43
13–18	452	2189	.009
2–18	1011	2073	.01

Abbreviation: PCR, polymerase chain reaction.

^a By the *t* test.

contrast between age groups with high and low pertussis incidences. We also selected the 13–18-year age group to reflect the vaccine dose recommended at ages 10–12 years.

RESULTS

We identified 171 individuals who were PCR positive for *B. pertussis*; 48% male and 52% female. There were no fatalities. Ages ranged from infancy to 90 years. Vaccine histories were generally unavailable for those aged >18 years, and these patients were therefore excluded. Of the 132 individuals (77.2%) aged ≤18 years at time of illness, 81% were fully vaccinated, 11% were undervaccinated, and 8% were never vaccinated. Of the 103 individuals (60.2%) aged ≤12 years, 85% were fully vaccinated, 7% were undervaccinated, and 8% were never vaccinated.

There were 22 798 patients aged ≤18 years in our patient population. In this group, vaccination rates across ages were excellent, ranging from 88%–94%. Among confirmed cases of pertussis, vaccination rates were comparable in the groups aged 2–7 years and 8–12 years, when contrasted with age-

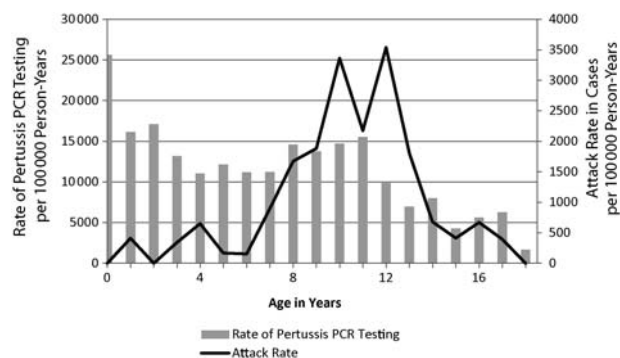


Figure 1. Pertussis attack rate and polymerase chain reaction testing rate. Abbreviation: PCR, polymerase chain reaction.

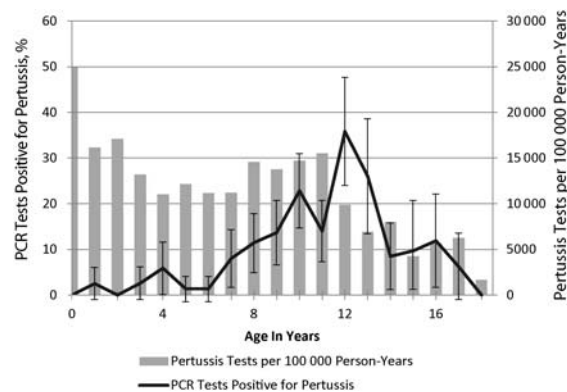


Figure 2. *Bordetella pertussis* testing rate and test positivity, by age. Abbreviation: PCR, polymerase chain reaction.

matched controls. Among the 58 cases of pertussis in children aged 10–12 years, 55 (95%) had received ≥5 doses of pertussis vaccination. Eight of these 58 children (14%) had received their sixth booster dose prior to onset of disease. In children aged 13–18 years and in the entire cohort of those aged 2–18 years, there was a highly significant increase in cases among unvaccinated children (*P* = .009 and .01, respectively; Table 1).

Rates of laboratory-confirmed clinical pertussis among fully vaccinated children showed a broad increase from ages 8 through 13 years. Calculated annualized attack rates among vaccination children, stratified by age, ranged from 0 cases per 100 000 persons-years, among patients aged 2 years, to 3666 cases per 100 000 person-years, among patients aged 12 years. This disparity was highly significant (*P* = .002, by the 1-sample *t* test; Figure 1). Nonannualized, age-specific attack rates among vaccinated children ranged from 0 cases per 100 000 population, among patients aged 2 years, to 1981 cases per 100 000 population, among patients aged 10 years.

During the study period, 1358 persons aged ≤18 years were tested for pertussis. The rate of laboratory testing for pertussis is shown in Figure 1. Testing rates were highest among infants but decreased among patients >12 years old. PCR positivity rates for pertussis are shown by age in Figure 2. The lowest rate was 2% and occurred among patients aged 2 years, and the highest rate was 36% (95% confidence interval, 24%–38%) and occurred among patients aged 12 years.

Vaccine effectiveness, determined on the basis of the screening method, was determined to be 41%, 24%, 79%, and 51% for patients aged 2–7 years, 8–12 years, 13–18 years, and 2–18 years, respectively [15] (Table 2).

DISCUSSION

Pertussis is one of the most prevalent vaccine-preventable diseases in the developed world [16]. Despite widespread

Table 2. Vaccine Effectiveness, by Age

Age, Years	PPV, %	PCV, %	Effectiveness, % (95% CI)
2–7	91	86	41 (21–54)
8–12	89	86	24 (0–40)
13–18	89	62	79 (73–84)
2–18	90	81	51 (44–58)

Abbreviations: CI, confidence interval; PCV, proportion of cases fully vaccinated; PPV, proportion of the population fully vaccinated.

childhood vaccination and a greatly reduced incidence, there are still many cases, with outbreaks peaking every 2–5 years [17]. The incidence in the United States has been estimated to be between 800 000 and 3.3 million cases per year [17]. The primary reason for these large numbers is believed to be a persistent reservoir of disease in adolescents and adults, which the revised CDC vaccine schedule sought to address [10, 11]. We found lower than expected protection from disease by the primary 5-dose series of acellular pertussis vaccine, suggesting that pertussis vaccine, administered according to the current guidelines, may not adequately protect the preadolescent and early adolescent populations.

Surprisingly, in the 2–7-year and 8–12-year age groups, there was no significant difference in attack rates between fully vaccinated children and both undervaccinated and unvaccinated children; however, the attack rate in the 2–7-year age group, vaccinated or not, was significantly lower than that in the 8–12-year age group ($P = .002$). The 13–18-year age group and the aggregate of all age groups did demonstrate a significantly increased risk for pertussis in the undervaccinated and unvaccinated group, possibly demonstrating the enhanced protection of the booster vaccination dose at the age of 12 years. There were 2 overnight admissions for observation, but no other hospitalizations were reported among our cohort, suggesting a mitigating effect of the current vaccine.

We noted a marked disparity between the lower attack rates among children aged <8 years and children aged >12 years and the higher attack rates for children aged 8–12 years. This difference was highly significant ($P = .002$). The sharp increase in the number of cases among children aged 8 years appears to correlate to the interval from the end of the preschool vaccine series. There is a decrease in the number of cases occurring at among those aged ≥ 13 years, corresponding to the booster dose given from ages 10–12 years (Figure 1). This is confirmed by examination of the mean interval from last vaccination, grouped by age, among our laboratory-confirmed clinical cases (Figure 3). These findings may be explained by the patterns of pertussis vaccination, which reflect ACIP recommendations and statutory requirements in California [8, 9, 18].

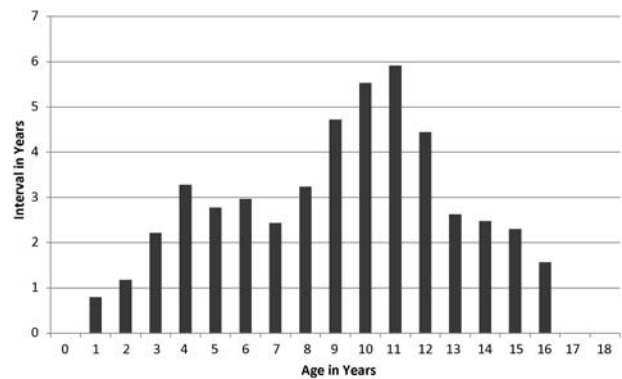


Figure 3. Mean interval between clinical presentation and receipt of the last scheduled acellular pertussis vaccine in fully vaccinated persons.

Our data suggest that susceptibility increases as the interval from the last scheduled vaccination increases. This would lead to a reduced level of herd immunity within an age group, resulting in greater risk of acquisition of disease by vaccinated yet unprotected individuals [19]. It also brings into question the durability of the immunity provided by the acellular pertussis vaccine.

Vaccine effectiveness calculations were performed using the screening method, which uses the odds ratio of full vaccination between cases and the general population to determine VE [15]. In this study, we were able to accurately determine the population vaccination rate and identify all cases within the patient population and their vaccination status. Our vaccine effectiveness data confirm markedly lower than expected protection afforded by the preschool series of acellular pertussis vaccinations in the 8–12-year age group.

It is important to note that our calculations of vaccine effectiveness were limited by the number of cases. Vaccine effectiveness, a useful metric for estimating vaccine performance, is not a substitute for traditional, placebo-controlled trials to determine true vaccine efficacy, and the values are not interchangeable [6, 15]. However, vaccine effectiveness can also be more useful than vaccine efficacy, when it comes to evaluating the success of a vaccine. Vaccine effectiveness quantifies easily and on a large scale the performance of the vaccine in a real-world environment.

It has been suggested that acellular pertussis vaccine may have reduced efficacy when contrasted with whole-cell pertussis vaccine [4, 9]. It has also been suggested that the acellular pertussis vaccine may have a reduced durability of immunity, and no vaccine trial has examined immunity from these vaccines beyond 22 months [2]. The recommendation for booster vaccination between 10 and 12 years of age may be too late to provide protection to this group.

Fortunately, the aggressive vaccination schedule for younger children appears to effectively protect those <5 years of age,

except infants <6 months of age, who remain vulnerable. High efficacy in the first year or two after primary vaccination is well documented [2, 20–22]. Transmission from parents has been recognized to be a high risk to infants, but older siblings may introduce the disease into a household and therefore also present a direct risk to the infants [23, 24]. This natural demography of familial transmission underscores the importance of our findings. We confirmed vaccine failures and probable decreased herd immunity among this group of preteens.

A final consideration involves the difference in vaccine performance between endemic pertussis and an outbreak situation. At-risk exposures are logarithmically increased during an outbreak, markedly enhancing the risk of acquisition of disease [19].

Most studies of clinical pertussis have been based on passive reporting to health departments, lack defined population denominators, and have potential selection bias in testing rates or methods. Our study examines a stable, defined population having well-recorded vaccination histories, a well-defined rate of disease, and uniformly documented laboratory testing. The practice agreement to test all prolonged cough-associated illness helps eliminate bias toward enhanced reporting of cases with complications or toward overreporting when all cough-associated illness is sampled. The high percentage of persons in our community who obtain their care solely from our medical center provides an ideal opportunity to examine a population. Reporting bias in our data is virtually eliminated by the structurally complete capture of patient data. If there were ascertainment bias, the rate of testing would suggest dampening, not accentuation, of the age-based differences in rates of disease in our population. However, since the rate of testing is relatively flat by age, ascertainment bias is likely minimal. The documentation of prior vaccinations permitted accurate ascertainment of vaccination status.

There were limitations to our study. It was retrospective. Many clinicians believe that pertussis vaccination is highly effective and, because of this, may not suspect or test for pertussis in vaccinated children [25]. Pertussis testing in our study was not part of a protocol, although the practice agreement sought to reduce effects of variance in clinician practices. Previous investigations have shown that that vaccination results in a shorter, less severe illness, which may have contributed to minor cases being missed and an underestimation of the pertussis incidence [26].

PCR testing was not confirmed by concomitant bacterial culture in our study; however, PCR testing has generally been demonstrated to be highly specific [27]. Difficulty discriminating certain strains of *Bordetella holmesii* or *Bordetella bronchiseptica* from *B. pertussis* and *B. paraptussis* has been recognized [28]. *B. holmesii* was unlikely to have been present in our population, as there were no specimens positive for both *B. pertussis* and *B. paraptussis*. Amplification of both sequences (IS481 and IS1001) would have been expected if *B. holmesii* were present, as

this organism contains both of these sequences in its genome [28, 29]. Among cases reported to the California Department of Public Health, there were no isolates of either *B. holmesii* or *B. bronchiseptica*, and *B. bronchiseptica* rarely causes disease in immunocompetent individuals [29, 30].

It is notable that, despite the high level of vaccine coverage in our population, relative to the United States, 11% of our children are not fully vaccinated; therefore, our population does not reach levels of protection required for herd immunity [31]. When contrasted to with rates of vaccination in European countries, our relatively high rate falls short [32].

This is the first review of clinical pertussis in a large North American outbreak since the acellular vaccine was introduced. It examined the frequency of disease in a closed, well-monitored population. We confirmed that the rate of vaccine failure increased as the interval from receipt of the primary vaccine series increased.

In the case of the recent California epidemic, it appears that the effectiveness of the current vaccine schedule, when paired with the imperfect vaccination rate, may be insufficient to prevent an epidemic. Earlier vaccine booster doses may be required to provide adequate herd immunity, absent an increase in vaccination rate, efficacy, or durability. Earlier booster doses could prevent immunity from waning and address disease among children aged 8–12 years. Recent recommendations from the ACIP have supported the safety of administration of Tdap to individuals as young as 7 years of age, regardless of prior vaccination histories [33]. Research into natural pertussis immunity and more durable and effective vaccines should be expanded. An earlier booster dose and targeted vaccine programs are strategies that should be entertained and could be vital to controlling widespread outbreaks of disease. Use of targeted vaccine programs in adolescence, rather than delivery of additional boosters defined by age, might be an alternative vaccination strategy that would address parental concerns regarding additional scheduled vaccine doses and increased cost. Further research is needed to evaluate the long-term efficacy of the acellular pertussis vaccine, as well as the potential benefits or adverse effects of introducing an earlier booster dose.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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