Reduced Risk of Pertussis Among Persons Ever Vaccinated With Whole Cell Pertussis Vaccine Compared to Recipients of Acellular Pertussis Vaccines in a Large US Cohort

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Background. Unexpected waning of immunity after pertussis vaccination is now well described. In this study we examined whether prior vaccination with whole-cell pertussis vaccine (wP) at any point provided superior protection contrasted with a solely acellular pertussis vaccine (aP) series. We utilized the coincidence of a large outbreak of pertussis with the termination of wP availability, providing populations of children who had been vaccinated with combinations of wP and aP.

Methods. Kaiser Permanente (KP) is an integrated healthcare system with complete electronic records and a centralized laboratory. Cases of laboratory-confirmed pertussis and vaccination data for members aged 8–20 years were retrieved.

Results. Among 263,496 persons aged 8–20 years, 904 cases of pertussis were identified. In patients with a full history of vaccinations administered by KP, those with 5 total doses of only aP had an 8.57 relative risk (RR) of pertussis ($P < .0001$) contrasted to those with ≥1 wP dose. With 6 doses of aP, the RR of disease was 3.55 ($P < .0001$). When external vaccine records were included, the results were similar.

Conclusions. We found a markedly increased risk of disease associated with an entirely aP series. This risk was mitigated, but not eliminated, by the presence of a sixth dose of pertussis vaccine (Tdap). Receipt of 1 or more wP doses markedly augmented the durability of immunity from subsequent aP doses. It appears that a wholly acellular pertussis vaccine series is significantly less effective and durable than one that contains the traditional whole cell vaccine.

Keywords. pertussis vaccine; whole cell pertussis vaccine; acellular pertussis vaccine; Bordetella pertussis.

We recently reported an unexpected waning immunity to pertussis vaccination among older preadolescents [1]. There have been prior suggestions that the efficacy of the acellular pertussis (aP) vaccine may not be as robust as reported in these initial studies [2–4]. The unexpectedly high attack rate in this age group has now been confirmed during outbreaks in the states of Washington, Wisconsin, and Minnesota as well as in the United Kingdom [5–8]. Possible reasons for apparent decreased efficacy of aP have been proposed, including observer bias in initial trials; reduced antigenic stimulation in aP; and even mutation of Bordetella pertussis [9].

Acellular pertussis vaccines were introduced in the United States in 1991 for use as a booster, but not until 1997 were they recommended for use in primary vaccination. When contrasted with whole cell pertussis (wP) vaccine, these vaccines have been assumed to be comparably efficacious while having markedly reduced adverse reactions [10]. For this reason, the acellular vaccine is now the sole pertussis vaccine used in the United States. Efficacy for the aP vaccine has been
reported as between 84% and 85% for children and 92% for adolescents and adults [10, 11].

In our initial study, there was a notable absence of disease in adolescents [1]. In the recent outbreaks in Washington, Wisconsin, and Minnesota, there also was a falloff in disease among those >13 years of age. We had also noted a trend toward higher rates of pertussis among children who had never received prior whole cell vaccine; however, the number of cases in this category was too limited to make conclusions [12]. Sheridan and colleagues examined their findings in Australia and suggested that receiving prior whole cell vaccination may explain an enhanced durability of immune response among older children [13]. With the unique converging opportunities presented by a pertussis outbreak in a well-vaccinated population and a changeover in vaccine recommendations with overlapping populations of children who had received either some or no wP, we sought to examine the effect of prior whole cell vaccination on the pertussis attack rate. We used our large integrated healthcare system with combined laboratory and clinical systems, an electronic medical record, and well-documented records of vaccinations administered to accurately ascertain rates of clinical pertussis and its relation to prior vaccination regimens.

METHODS

Approval for the study was obtained from the Institutional Review Board of the Kaiser Foundation Research Institute (Oakland, California). 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. Kaiser Permanente in Northern California is the primary source of care for 3.4 million persons.

Nasopharyngeal specimens for pertussis testing were obtained using a BD BBL Culture swab with liquid Stuart media (catalog number 220133; Becton, Dickinson and Co, Franklin Lakes, New Jersey) and sent for centralized laboratory testing. Real-time polymerase chain reaction (PCR; Cepheid Corporation, Sunnyvale, California) 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.

Vaccines used since 2002 included Infanrix, Pediarix, and Boostrix (GlaxoSmithKline, Research Triangle Park, North Carolina) and Daptacel, Pentacel, and Adacel (Sanofi Pasteur, Bridgewater, New Jersey).

Because aP was introduced in 1991 and wP was retired from use in the United States in 2001 and at Kaiser in 1999, we selected patients born during the years 1990–2001. This population was old enough to have received wP vaccine and young enough to have received aP vaccine. We parsed the data to compare rates of disease in patients with specific vaccination histories.

Cases were defined as the presence of a positive PCR test for B. pertussis and a negative PCR test for B. parapertussis. Data were obtained for active members aged 8–20 years as of 15 May 2010, a date at the peak of the California pertussis epidemic. Records on all pertussis vaccines administered were obtained and entered into IBM SPSS (IBM, Armonk, New York) statistics for analysis. Vaccination type, the number of doses of each (wP or aP), and the origin of vaccine documentation (administration documented within the Kaiser Permanente system or entered from outside records) was retrieved. Cross-tabulated SPSS output data was entered into Microsoft Excel (Microsoft, Redmond, Washington) for further analysis.

In one analysis, members were included if they were 8–20 years of age as of 15 May 2010 or if they had a positive PCR test result from 1 January 2006 to 15 November 2011 and had received 5 or 6 doses of pertussis vaccine administered by Kaiser Permanente at the time of disease. For a second analysis, inclusion criteria were broadened to include those who had received 1 or more pertussis vaccine doses at Kaiser Permanente, and at least 5 or 6 total vaccine doses, including vaccinations administered outside the Kaiser Permanente system, recorded in the Kaiser Permanente vaccine database. To be considered as having received a dose of wP, doses of wP must have been administered at Kaiser Permanente.

RESULTS

Of a total population of 3.2 million members, there were 263,496 persons aged 8–20 years. Among this population, 904 cases of pertussis were identified. In patients with a full history of vaccinations administered by Kaiser Permanente, the results were as follows and are detailed in Table 1. For those with 5 doses of pertussis vaccine, having had no doses of whole cell vaccine was associated with an 8.57 relative risk of pertussis ($P < .0001$) when compared to those who had received 1 or more dose of whole cell vaccine. For those with 6 doses, those who received only acellular vaccine had a 3.55 relative risk of disease ($P < .0001$) contrasted to those with a history of whole cell vaccines. In the combined 5- and 6-dose groups, those who received only acellular vaccines had a 5.47 relative risk of disease compared to those with 1 or more whole cell dose ($P = .001$).

In patients with at least 1 pertussis vaccine administered by Kaiser Permanente, the results were similar but slightly attenuated when contrasted with those who received all vaccines...
within the Kaiser Permanente system. These results are detailed in Table 2. For those with 5 doses of pertussis vaccine, having had no doses of whole cell vaccine was associated with a 6.76 relative risk when compared to those with 1 or more doses of whole cell vaccine (P < .0001). For those with 6 doses, those who received only acellular vaccine had a 2.46 relative risk compared to those with a history of whole cell vaccines (P = .0002). In the combined 5- and 6-dose groups, those who received only acellular vaccines had a 3.81 relative risk of disease, contrasted to those who had received 1 or more whole cell doses (P < .0001).

In those who received 5 total doses of vaccine, the mean interval from last vaccination, among cases, was 14.7 (SD, 3.23) and 5.65 (SD, 0.24) years for wP and aP, respectively. For those receiving 6 total doses, the interval was 3.07 (SD, 2.28) and 1.54 (SD, 0.47) years, for wP and aP, respectively. (Figure 1)

The type of vaccine received and the distribution of confirmed cases of pertussis are presented by age in Table 3. This table shows the near complete substitution of acellular pertussis vaccine as a primary vaccine series once available and recommended in this role in 1997 and demonstrates the reduced rate of cases among those who have received the whole cell vaccine.

**DISCUSSION**

Pertussis remains one of the most prevalent vaccine-preventable diseases in the developed world [12]. Despite widespread childhood vaccination and a greatly reduced incidence, there are still many cases, with outbreaks peaking every 2–5 years [14]. It has been suggested that aP vaccine may have reduced efficacy when contrasted with wP vaccine [2, 15]. It has also been suggested that the aP vaccine may have a reduced durability of immunity, and no vaccine trial has examined immunity from these vaccines beyond 22 months [10].

In a prior study, we found lower than expected durability of protection from disease by the primary 5-dose series of aP vaccine. This suggests that pertussis vaccine, administered according to the current guidelines, may not adequately protect the preadolescent and early adolescent populations [1]. It was notable that the attack rate of pertussis during the outbreak in California in 2010 was markedly less in adolescents, whether or not they had received the Tdap booster. This would temporally correlate to the introduction of the aP vaccine in 1991, which had completely supplanted vaccination with wP vaccine in the United States by 2001. Thus, all children born after 2001 would have had only aP vaccine, whereas those born in the preceding 10 years may have had some combination of the 2 vaccine types. This period of overlapping vaccine practices provided an opportunity to examine relative effectiveness of
these 2 vaccines among persons born during this time period. The pertussis outbreak of 2010 permitted examining the relative effectiveness during a high-density exposure.

Our current results confirm a profoundly enhanced protection from pertussis for all persons who had ever received a dose of wP vaccine, when contrasted with those who had received only aP. This effect persisted for years, demonstrated by an enhanced effectiveness of Tdap in those who had received wP vaccine as part of their primary series of pertussis vaccination. Increased efficacy of wP vaccine, contrasted with aP vaccine, has been previously suggested [2]. Reasons for this may include variations in antigenic composition of vaccine, blocking effects of antibody to some vaccine antigens, and even genetic changes in circulating \textit{B. pertussis} strains [14]. We have also identified that this increased effectiveness extends to enhancing the effectiveness of subsequent vaccination with aP.

We found a markedly increased risk of disease associated with an entirely acellular pertussis vaccine series. This risk was mitigated, but not eliminated, by the presence of a sixth dose of pertussis vaccine (Tdap). It appears that a solely acellular pertussis vaccine series is significantly less effective and durable than one that contains the traditional whole cell vaccine.

It was necessary to calculate a relative risk of pertussis contrasting those who had received wP vaccine and those who had not. Actual vaccine effectiveness (VE) could not be reliably calculated, as VE requires contrasting vaccinated groups with unvaccinated groups [16]. While those who are vaccinated within the Kaiser Permanente system have clear records with perfect ascertainment of vaccination status, those with no vaccinations recorded or vaccinations outside of the Kaiser Permanente system included persons who had never accessed care, never had a primary care appointment, or could not provide documentation of prior vaccination. This apparently totally unvaccinated group is quite small and may, in fact, be composed of enough vaccinated persons who do not have vaccination documented to make this group unworkable as a comparison group for the wholly vaccinated and completely documented groups in the calculation of VE. For this reason we examined only persons with recorded vaccination records. Undervaccinated persons and unvaccinated persons were thus excluded from analysis as well, for the same reasons.

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 with well-documented vaccination histories, a well-defined rate of disease, and uniformly documented laboratory testing. The high percentage of persons in our community who obtain their care solely from our medical centers provides

<table>
<thead>
<tr>
<th>Vaccine Received</th>
<th>Pertussis Cases</th>
<th>Members</th>
<th>AR per 100,000</th>
<th>Relative Risk aP Only/wP ≥1 Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>aP only</td>
<td>373</td>
<td>42,966</td>
<td>867.5</td>
<td>6.76</td>
</tr>
<tr>
<td>wP ≥1 dose</td>
<td>254</td>
<td>100,069</td>
<td>253.9</td>
<td>2.46</td>
</tr>
<tr>
<td>Combined wP</td>
<td>397</td>
<td>149,035</td>
<td>671.0</td>
<td>2.21</td>
</tr>
</tbody>
</table>

Abbreviations: aP, acellular pertussis vaccine; AR, attack rate per 100,000 population; KP, Kaiser Permanente; wP, whole cell pertussis vaccine.
an ideal opportunity to examine a population. Reporting bias in our data is markedly reduced by the structurally complete capture of patient data. The documentation of prior vaccinations permitted accurate ascertainment of vaccination status.

There were limitations to our study. It was retrospective. Prior vaccination results in a shorter, less severe illness, which may have contributed to minor cases being missed, leading to an underestimation of the pertussis incidence [17]. Pertussis testing was at the discretion of the clinician, permitting some degree of selection bias. PCR testing was not confirmed by concomitant bacterial culture in our study; however, PCR testing has generally been demonstrated to be highly specific [18]. Difficulty discriminating certain strains of Bordetella holmesii or Bordetella bronchiseptica from B. pertussis and B. parapertussis has been recognized [19]. B. holmesii was unlikely to have been present in our population, as there were no specimens positive for both B. pertussis and B. parapertussis. 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 [19, K. Harriman, written communication, September 2011]. In addition, 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 [K. Harriman, written communication, September 2011, 20].

Even if the un- and undervaccinated groups could be accurately identified from our database, we would still have limitations in the inability to calculate actual VE because we are not utilizing a single vaccine in the vaccine series, as would be theoretically required for a VE calculation [16]. We believe that this limitation is of limited significance if one examines the pertussis vaccine as a complete series of vaccines. Because there has not been, and likely never will be, a long-term study of aP vaccine, wP vaccine, or a combination of the 2, in our opinion this approximation is as accurate an evaluation of the effectiveness of these vaccines as will ever be achieved. It is also worth noting that the vaccine schedule for aP was adapted to that of the traditional wP schedule, but had not been studied for the complete 5-dose series, and that for the later doses, often the initial vaccine doses had been wP [21].

The effect of the force of illness must also be considered. Higher exposure rates would be expected to lead to higher rates of disease. Although this might have contributed to an amplification of the attack rate we observed in preadolescent children, the low rate of disease in both younger children and particularly in older teens, who had the longest interval from prior vaccination, remains highly significant. This distribution of cases, with the preadolescent peak visible, is shown in Table 3. Preadolescent peaks similar to the one we identified are observed in the current outbreaks worldwide [5, 6, 7, 8, 22]. Observations of increasing rates of pertussis in preteens and
adolescents in the era prior to aP still demonstrated the predominance of infection in infants and the youngest children, with a smoothly decreasing rate associated with age. There clearly has never previously been a peak of infection in the preadolescent group [23]. The fact that the vast bulk of these infections occurred in fully vaccinated children only emphasizes the limited durability of immunity in this group, the first vaccinated solely with acellular vaccine. The low rate of pertussis in the older teens reflects the patterns observed in the era prior to aP. Our findings of higher effectiveness of wP primary vaccination, including augmentation of effectiveness of subsequent aP boosters, contributes to herd immunity in this age group and thus force of infection was lower, reflective of this enhanced immunity.

In summary, we have confirmed a decreased protection from aP vaccine when contrasted with wP vaccine. We also identified a long-term enhancement of protection from aP in those who have ever received prior wP as part of their primary series. The implications of these findings are significant. The current generation of children is the first generation to have been vaccinated solely with aP. Waning immunity is even more severe if they have never received wP. It is of note that widespread pertussis outbreaks have been occurring in the United States for the last 3 years. The peak attack rates are among those who are in this exact group—those solely vaccinated with aP. Younger children are protected by the more frequent doses of aP administered to this age group, but immunity has limited durability [1]. This finding of waning immunity associated with ongoing outbreaks of pertussis argues for earlier booster doses of aP vaccine, on a routine basis and particularly in an outbreak setting, and clearly is a call for development of more effective and durable pertussis vaccines.

**Note**

**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.

**References**

