Kinetics of Pertussis Immune Responses to Tetanus-Diphtheria-Acellular Pertussis Vaccine in Health Care Personnel: Implications for Outbreak Control

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(See the editorial commentary by Birkebaek on pages 588–90)

We assessed the kinetics of the humoral immune response to pertussis antigens following vaccination of health care personnel with adult tetanus-diphtheria-acellular pertussis vaccine (Tdap). By 2 weeks after vaccination, 88%–94% of subjects demonstrated a booster response. This brisk response of adults to Tdap supports a role for vaccination in pertussis outbreak control.

Pertussis outbreaks among health care personnel pose substantial risks to patients, especially infants, and outbreak control can be costly and disruptive to medical centers [1–3]. Until the 2005 licensure of adult tetanus and diphtheria toxoids combined with acellular pertussis vaccine (Tdap), pertussis control efforts in the hospital centered on early detection, isolation of infected persons, and prompt postexposure prophylaxis for their immediate contacts. Because the clinical and laboratory diagnosis of pertussis can be challenging, particularly in adults, prevention of pertussis through vaccination of health care personnel is an attractive option [4]. Moreover, vaccination of health care personnel protects patients (particularly vulnerable infants and elderly) from the risk of nosocomial pertussis.

Soon after Tdap licensure, routine vaccination was recommended for all health care personnel by the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention [5]. Prelicensure studies of Tdap in adults demonstrated robust immune responses at 4 weeks after vaccination [6]. However, the kinetics of the immediate immune response to vaccine have not been well characterized, and it is uncertain whether immediate vaccination of health care personnel at the time of an exposure might confer protection. The occurrence of an outbreak of pertussis-like illness at our medical center in April 2006 resulted in an extensive vaccination campaign among health care personnel and offered the opportunity to assess the kinetics of the humoral immune response to Tdap.

**Methods.** Asymptomatic health care personnel, including physicians, staff, and volunteers, were encouraged to receive Tdap vaccine and were invited to participate in this study. After obtaining informed consent, demographic data were collected, including age, sex, and history of previous childhood vaccination with diphtheria and tetanus toxoids and acellular or whole-cell pertussis vaccine (DTP).

Each participant received a single 0.5-mL dose of Tdap (Adacel; Sanofi Pasteur) administered into the deltoid muscle. Active ingredients include 5 Lf tetanus toxoid, 2 Lf diphtheria toxoid, 2.5 µg pertussis toxoid, 5 µg filamentous hemagglutinin, 3 µg pertactin, and 5 µg fimbriae types 2 and 3.

Serum specimens were collected immediately before vaccination and again at 1, 2, and 4 weeks after vaccination. At each visit, participants were questioned regarding the development of a respiratory illness since the last visit.

Sera were stored at −20 °C until all specimen collection was completed and were then shipped together on dry ice to Sanofi Pasteur laboratories. Standard enzyme-linked immunosorbent assays for antibody to pertussis toxoid, filamentous hemagglutinin, pertactin, and fimbriae types 2 and 3 were performed at the Sanofi Pasteur laboratories, and geometric mean concentrations were measured. The lower limit of quantitation (LLOQ) for the pertussis antigens were 4 EU/mL for pertactin, fimbriae, and pertussis toxoid and 3 EU/mL for filamentous hemagglutinin. Booster response rates were calculated as follows. If the prevaccination level was less than the LLOQ, then a postvaccination level ≥4 times the LLOQ was considered to be a booster response. If the prevaccination level was greater than or equal to the LLOQ but less than 4 times the LLOQ, then a ≥4-fold increase was considered to be a boost-
Table 1. Geometric Mean Concentrations (GMCs) and Booster Responses among 106 Health Care Personnel after Tdap Vaccine

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Prevaccination GMC, EU/mL (n = 106)</th>
<th>1 Week postvaccination GMC, EU/mL (n = 100)</th>
<th>Booster response, %</th>
<th>2 Weeks postvaccination GMC, EU/mL (n = 100)</th>
<th>Booster response, %</th>
<th>4 Weeks postvaccination GMC, EU/mL (n = 97)</th>
<th>Booster response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertussis toxin</td>
<td>13.5</td>
<td>48.3</td>
<td>46.4</td>
<td>112.0</td>
<td>87.7</td>
<td>109.5</td>
<td>84.0</td>
</tr>
<tr>
<td>Filamentous hemagglutinin</td>
<td>21.9</td>
<td>85.1</td>
<td>68.9</td>
<td>204.2</td>
<td>94.0</td>
<td>226.7</td>
<td>99.0</td>
</tr>
<tr>
<td>Pertactin</td>
<td>10.7</td>
<td>65.3</td>
<td>62.1</td>
<td>236.4</td>
<td>88.0</td>
<td>254.3</td>
<td>89.7</td>
</tr>
<tr>
<td>Fimbrial agglutinogens</td>
<td>29.3</td>
<td>285.3</td>
<td>79.6</td>
<td>627.0</td>
<td>93.0</td>
<td>587.5</td>
<td>94.8</td>
</tr>
</tbody>
</table>

er response. If the prevaccination level was ≥4 times the LLOQ, then a ≥2-fold increase was considered to be a booster response.

The study protocol was approved by the Dartmouth College Committee for the Protection of Human Subjects. All subjects provided written informed consent prior to participation in the study.

**Results.** One hundred fifteen subjects were enrolled during 5–8 May 2006. The median age of the 115 enrolled subjects was 45 years (range, 19–79 years), including 23 subjects aged ≥55 years; 67 (58%) were female, 91 (79%) reported having received a prior DTP, 3 (3%) denied receiving a prior DTP, and 21 (18%) were unsure of their DTP history. None of the study subjects reported a respiratory illness at any time during the 4-week study period.

One hundred six subjects (92%) had a prevaccination sample and at least 1 postvaccination sample available for antibody testing. Of these 106 subjects, 103 (97%) had sera obtained at 1 week, 100 (94%) had sera obtained at 2 weeks, and 97 (92%) had sera obtained at 4 weeks after vaccination. Overall, 94 subjects (89%) had all 4 specimens available for evaluation.

Antibody responses to each of the pertussis antigens are shown in table 1. By 1 week after vaccination, more than one-half of the subjects showed booster responses to filamentous hemagglutinin, pertactin, and fimbriae, and 46% showed a booster response to pertussis toxoid. By 2 weeks after Tdap vaccination, the proportion of subjects that demonstrated a booster response ranged from 88% to 94%, depending on the specific pertussis antigen. By 4 weeks, a booster response to at least 3 antigens was achieved by 92% of subjects, and 66% had

Figure 1. Reverse cumulative distribution curves of pertussis antibodies titers before (week 0) and 1, 2, and, 4 weeks after Tdap vaccination. FHA, filamentous hemagglutinin; fimbriae, fimbriae types 2 and 3; pertactin, pertactin; PT, pertussis toxoid.
booster responses to all 4 antigens. There were no significant differences between subjects aged <55 years and those aged ≥55 years in the proportion demonstrating booster responses to at least 3 antigens (94% vs 87%; \( P = .4 \)) or to all 4 antigens (66% vs 65%; \( P = .9 \)). Only 1 subject failed to manifest a booster response to any of the antigens. For this 56-year-old woman, prevaccination levels of all 4 antibodies were >4 times the LLOQ, and only the 1-week postvaccination serum sample was available for testing.

Reverse cumulative distribution curves for the 4 pertussis antigens are presented in figure 1. Population antibody responses were nearly identical at 2 and 4 weeks after vaccination. Not only are the later-week reverse cumulative distribution curves shifted substantially to the right of the week 0 reverse cumulative distribution curves, indicating higher individual and population antibody levels, but they are also more rectangular than the week 0 reverse cumulative distribution curves, indicating reduced variability in antibody level within the population.

Discussion. Our data on the early kinetics of Tdap vaccination supplement data obtained before licensure demonstrating that booster responses in adults are achieved by 4 weeks after vaccination [6] and expand these observations by measuring responses at earlier intervals as well. In our group of adult health care personnel, Tdap-induced pertussis antibody responses were brisk and clearly noticeable by 1 week after vaccination, peaking at 2 weeks after vaccination, which suggests that early Tdap vaccination may be valuable to prevent illness and transmission among adults in pertussis outbreak settings.

All licensed acellular pertussis vaccines contain pertussis toxoid; most also contain filamentous hemagglutinin, some contain pertactin, and a few include fimbriae. Efficacy trials suggest that these vaccines may differ in the protection offered, but the experiences of national vaccine programs that have adopted different vaccines have demonstrated that each is capable of controlling pertussis if deployed in an effective vaccination program [7]. Efforts to find serologic correlates of immunity to pertussis among populations receiving various acellular or whole cell pertussis vaccines have suggested that having an adequate level of antibody to pertussis toxoid is important for protection when levels of antibody to pertactin and fimbriae are low; when pertactin or fimbriae antibody levels are adequate, the level of antibody to pertussis toxoid is less important; and having adequate antibody to both pertactin and fimbriae provides the best protection [8]. For this reason, we opted to assess postvaccination antibody responses to all 4 major pertussis antigens. Our finding that the majority of subjects developed booster responses to all 4 antigens by 2 weeks after vaccination supports our conclusion that immunity to pertussis develops quickly in adults who receive Tdap.

Pertussis outbreaks in health care settings typically are prolonged because they involve groups of adults whose immunity to pertussis has waned and who are in frequent close contact with one another, allowing multiple opportunities for transmission. Traditional public health interventions that involve isolation of both confirmed and suspected cases, with post-exposure prophylaxis for close contacts, can be quite disruptive to medical centers, especially those that operate near full capacity and depend on full staffing to maintain normal operations [1–3, 9, 10]. As we found in our outbreak of pertussis-like illness, initiation of active screening can lead to identification of many health care personnel who are working despite mild or moderate respiratory symptoms, many of whom have illnesses other than pertussis [11]. Requiring their exclusion from work, even if only during the time needed to rule out pertussis by the use of molecular techniques, can have a major impact. However, allowing potentially contagious health care personnel to continue to provide patient care can place patients at risk and spread illness to other staff, leading at a minimum to prolongation of the outbreak and perhaps to more dire consequences.

Clearly, universal Tdap vaccination for all health care personnel before pertussis cases occur, as recommended by ACIP, is the optimal strategy for preventing pertussis outbreaks in medical centers. However, implementation of universal vaccine campaigns among employees already working in a medical center can be challenging. Our study, although limited to a relatively small number of health care personnel in 1 locale, suggests that Tdap vaccination of health care personnel early in a suspected outbreak is likely to reduce the susceptibility of the vaccinated health care personnel population within 1–2 weeks and should be considered as part of a comprehensive pertussis outbreak control strategy. Although it does not obviate the need to exclude infected health care personnel and, absent further evidence, to provide postexposure prophylaxis for contacts, it may reduce the duration that these measures are needed, thus saving resources and allowing a quicker return to normal operations.

Outside of health care, there may be opportunities for the early use of Tdap for adults involved in school or community outbreaks. Further studies would likely show similar early antibody kinetics among children and adolescents who receive Tdap boosters, potentially expanding the applicability of Tdap as a part of pertussis outbreak control.\[586 • CID 2009;49 (15 August) • BRIEF REPORT]
Pasteur to perform serologic assays for pertussis, receives funding from CSL, Wyeth, and Novartis to study unrelated vaccines, and is a consultant to PATH. M.D.D. is an employee of Sanofi Pasteur, the manufacturer of the Tdap used in this study. K.B.K. and E.A.T.: no conflicts.

References