Title

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Journal

Clinical Infectious Diseases, 61(11)

ISSN

1058-4838

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Publication Date

2015-12-01

DOI

10.1093/cid/civ700

Peer reviewed

The Effect of Tdap Vaccination of Pregnant Women on the Subsequent Antibody Responses of Their Infants

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(See the Major Article by Ladhani et al on pages 1637–44.)

Keywords. Tdap; pregnancy; antibody responses; United Kingdom; North America.

During the 20th century, *Bordetella pertussis* was extensively studied in animal models, and many toxins and protective antigens were described [1–3]. A leader in *B. pertussis* research was Margaret Pittman, who was at the National Institutes of Health/US Food and Drug Administration (NIH/FDA) from 1936 to 1990. She published 2 articles on pertussis toxin (PT) and the concept that pertussis was a toxin-mediated disease [4, 5]. In the 1970s, there was great concern about diphtheria, tetanus toxoids, whole-cell pertussis (DTwP) vaccines in many countries (including Sweden, West Germany, United Kingdom, and Japan) and their relationship to neurological illness and brain damage. The views of Dr Pittman led to the idea that less reactogenic acellular vaccines could be produced. Yuji Sato, who trained at NIH/FDA and was influenced by Dr Pittman, returned to Japan and developed the first Diphtheria, Tetanus and Pertussis (DTaP) vaccines [1]. His goal was to produce a PT toxoid vaccine; however, the initial vaccines developed in Japan contained, in addition to toxoided PT, filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae 2 (FIM 2) in varying amounts. In the 1980s, a number of acellular DTaP vaccines were developed and phase 2 studies were carried out. In the early 1990s, 8 efficacy trials were carried out in Europe and Africa. The trial vaccines contained different concentrations of 1 to 5 antigens. However, all of the vaccines contained virtually no lipopolysaccharide, and they were less reactogenic than the DTwP vaccines that they were compared with.

In their discussion, Ladhani and associates [6] state that in regard to pertussis, there are no pertussis antibody levels that correlate with protection. I believe this is not true. There are serologic correlates. However, since they did not support the concept of PT being the most important antigen, they have been generally ignored. Of the 8 efficacy trials carried out in the 1990s, only 2 were done in such a way that serological correlations could be determined [7, 8]. One of those studies was done by our group in Germany and the other was done in Sweden. The studies were performed independently, but the findings were similar. However, the study in Sweden had more power because there were approximately 2½ times as many exposed children. It was found that if the exposed children had low levels of antibody to PRN and/or to FIM 2 or FIM 2/3, they were protected approximately 70% of the time. In contrast, it was found that antibody to FHA had no protective role and antibody to PT in low levels played a minor role in the protection of these children aged 7 to 30 month.

The next point to discuss is the role of transplacentally acquired antibodies in the protection of infants aged ≤2 months. Pertussis toxin is made up of 2 subunits. The A subunit contains the ADP-ribosylating toxin and the bigger B subunit provides considerable efficacy against typical pertussis [1, 3]. The A subunit of PT is the cause of death in young infants [9–13]. PT (the A subunit) causes leukocytosis with lymphocytosis, and it has been suggested that the aggregates of leukocytes in the small arterioles and veinules are responsible for irreversible pulmonary hypertension, which leads to shock, organ failure, and death [9–13]. It is possible, however, that the leukocytosis is only a marker for the problem and not the direct cause. The adverse effect of PT on G proteins in the heart or lungs could possibly directly result in heart or respiratory failure [9, 10].

Nevertheless, small amounts of antibody to the A subunit of PT will prevent death in infants although it will not prevent infection. Therefore, the prevention of deaths by maternal tetanus, diphtheria and pertussis (Tdap) immunization in

Received 28 July 2015; accepted 3 August 2015; electronically published 15 September 2015.

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Clinical Infectious Diseases® 2015;61(11):1645–7

DOI: 10.1093/cid/civ700

the 2 UK studies is not unexpected [14, 15]. The effectiveness, however, was likely exaggerated because of the failure to look for mild as well as typical disease.

The first question to address relates to the risk of severe pertussis in DTaP vaccine recipients who have not had a booster immunization in the second year of life and who had a blunted immune response because of transplacentally acquired maternal antibody. Data from the United Kingdom suggest that this is not a problem [16]. This is explained by the fact that once a person has an antibody response to PT (either by immunization or infection), he or she, upon exposure, has a rapid recall of antibody to PT and so leukocytosis with lymphocytosis does not occur [2, 13]. Also, since antibody to the B subunit of PT is also recalled rapidly, children are protected against typical pertussis.

However, the situation in countries that use the Expanded Program on Immunization (EPI) schedule is different because these are usually developing countries and the vaccines used are whole cell vaccines (DTwP). In the United States in the early 1990s, there was consideration by the Advisory Committee on Immunization Practices (ACIP) to discontinue the DTwP dose in the second year of life. However, at an ACIP meeting, I spoke against this proposal. Support for my view was the fact that in England and Wales from 1988 through 1991, 29.7% of reported cases occurred in children aged 2 to 4 years. In contrast, US data (1989–1991) noted that only 12.6% of the reported cases occurred in those aged 2 to 4 years.

In a DTaP and DTwP pilot study in Germany in 1991, our group had the opportunity to examine the effect of transplacentally acquired antibody on the antibody responses following the third dose of the primary immunization series [17]. We found that a pre-immunization value of >0.5 EU/mL significantly lowered the immune response to PT but not to FHA, PRN, or FIM 2. Since the transplacentally acquired antibody values would be considerably higher following maternal immunization, this could be of future concern relating to the severity of pertussis in infants vaccinated at 6, 10, or 14 weeks of age (EPI schedule) without a booster dose in the second year of life.

The second major issue presented by Ladhani et al [6] is the possible blunting effect of high titers of transplacentally acquired antibody to tetanus and diphtheria toxins on the efficacy of the routinely used conjugate vaccines. This should be a nonissue in North America, but it is an issue in the United Kingdom. Perhaps, authorities in the United Kingdom should consider giving booster doses in the second year of life for Hib, meningococcal conjugate vaccine (MCC), and pneumococcal conjugate vaccine (PCV-13) vaccines. This could also be a concern in countries that use the EPI schedule. Important in this regard is the fact that DTwP vaccines throughout the world contain varying amounts of tetanus and diphtheria toxoids. In our study in Germany, with the Lederle DTwP vaccine (containing 12.5 Lf of diphtheria toxoid and 5.0 Lf of tetanus toxoid), the immune response to tetanus toxin was suppressed by a high (>0.1 IU/mL) pre-immunization value. The immune response to diphtheria toxin was not suppressed by a high pre-immunization value.

In summary, the use of Tdap in all pregnant women can be expected to prevent virtually all pertussis deaths in young infants. The effect of this maternal immunization on the blunting of the immune response following routine immunizations is not a particularly important problem relating to the risk of vaccine preventable diseases. However, any problem that may exist can be prevented by booster doses of DTaP, Hib, MCC, and PCV-13 in the second year of life.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has 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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