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Editorial

Pertussis outbreaks and pertussis vaccines: New insights, new concerns, new recommendations?

The U.S. and many other industrialized countries are experiencing continuing large-scale pertussis outbreaks. While cyclical outbreaks of this endemic disease are apparent, the size and scale of the current outbreaks over the last 3 years is notable. In the U.S., well over 18,000 cases have now been documented – outbreaks larger in scope than in the last 50 or more years – and these are certainly just the tip of the iceberg. At least 10 children are known to have died in California as a result of pertussis. Thus far in 2012, another eight children have died in the U.S. due to pertussis [1]. A recent report from the state of Washington notes over 2520 cases from January to August 2012, a rate of 37.5 cases per 100,000 population, resulting in a 1300% increase in the number of cases compared with 2011, and the largest number of cases in seven decades [1]. Notably, between 43% and 76% of subjects for whom vaccination history was available were up to date on DTaP or Tdap immunization [1]. These data are generally reflective of outbreaks throughout the U.S., and raise the question of what the root cause(s) of these outbreaks might be.

Reasons for the ongoing pertussis outbreaks in the U.S. likely include the following:

- Secondary vaccine failure (i.e., waning immunity).
- Possible skewing of pertussis immune responses in children due to use of the acellular pertussis vaccine in early childhood.
- Possible vaccine-resistant *B. pertussis* strains.
- Inadequate and confusing Tdap immunization recommendations and guidelines, resulting in underuse of the vaccine.
- Lack of awareness of need for tetanus–diphtheria–acellular pertussis (Tdap), specifically among adults, and anti-vaccine sentiment, leading to inadequate pertussis vaccine coverage levels in the population (i.e., lack of herd immunity).
- Unprecedented population mixing on a global scale (i.e., opportunity for exposure).
- High transmissibility of *Bordetella pertussis*.
- Improper handling of the vaccine, resulting in poor vaccine immunogenicity, and disease susceptibility (http://oig.hhs.gov/oei/reports/oei-04-10-00430.asp).

While each factor undoubtedly contributes to the cases and epidemics observed, the first four are of most interest and will be discussed below. While failure to get the vaccine due to anti-vaccine sentiment is an important issue, I have previously commented on the anti-vaccine movement [2–4].

1. Secondary vaccine failure

Waning vaccine immunity is a particularly interesting and important issue. Current data suggest that, in fact, this may be an important issue in the current widespread outbreaks. A growing body of evidence suggests that immunity induced by acellular pertussis vaccines is less durable than that induced by whole cell vaccines [5,6]. Importantly, Tdap vaccines were licensed in the U.S. based on serologic bridging studies, not efficacy studies, where comparisons with immune responses to DTaP in infants were made. Subsequent efficacy studies of acellular pertussis vaccines were of limited duration.

Data supporting differential disease rates among acellular vs. whole cell immunized children/adolescents are available. The most recent report is from a large study in California demonstrating that protection against pertussis among children waned within the 5 years after the fifth dose of DTaP [7]. Another report from Australia evaluating pertussis disease rates among over 40,000 children who had documentation of having received at least three doses of a pertussis-containing vaccine demonstrated a significantly higher rate (annual rate of 373.1 vs. 113.3 per 100,000, or a rate ratio 3.29 per 100,000 per year) among children who received 3 doses of DTaP, than among children who received DTwP, respectively [8]. Other studies have also observed increasing rates of susceptibility/disease with increasing time since immunization with acellular pertussis vaccines [6].

Underlying these findings may be the issues discussed below; in particular, the issues of immune response imprinting by a skewing of the immune response toward Th2 type responses, while inducing relatively poor Th1 long-term cellular immune responses.

2. Skewing of vaccine-induced immune responses due to acellular vaccine

Another issue requiring more research is the issue of possible skewing of the immune response in infants given acellular pertussis vaccines. Two acellular pertussis vaccines are used in the U.S.: vaccines that contain three pertussis components – pertussis toxin (Ptx), pertactin (Prn), filamentous hemagglutinin (Fha); and vaccines that contain five components – Ptx, Prn, Fha, fimbrial antigen 2 (Fim2), and fimbrial antigen 3 (Fim3). These vaccines produce high titers of antibodies to each component. Whole cell vaccines, on the other hand, produce lower levels of antibodies against a very

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broad, and larger, range of proteins and toxoids contained within the vaccine.

Mascart et al. have demonstrated that among 6 month-olds who received a primary pertussis series (age 2–4 months) with acellular vs. whole cell pertussis-containing vaccines, that Th2 imprinting occurred resulting in a Th2 skewed immune response [9]. This provides some evidence that the Th1/Th2 balance in response to pertussis vaccine may be determined by whether a whole cell or acellular pertussis vaccine was received as the initial series at an early age. Similarly, Rowe et al. have also demonstrated that immune responses to acellular pertussis vaccine among infants immunized at 2, 4 and 6 months are Th2 skewed [10]. The consequences may be that children receiving acellular vaccines are at a long-term disadvantage (i.e., increased susceptibility to disease with exposure) compared to those receiving whole cell vaccines, due to a real or relative lack of Th1 cellular memory immune responses.

3. Vaccine-resistant *B. pertussis* strains

The hypothesis of vaccine itself resulting in a mutational selective pressure and resulting in vaccine-resistant *B. pertussis* strains is an interesting one. Investigators in Australia have identified newly emerging *B. pertussis* clones among isolates from Australian outbreaks [11]. In particular, SNP cluster I strains increased from 31% of isolates (2000–2007) to 86% of isolates from 2008 to 2012, suggesting selection of pertussis strains that carry antigens not contained within the acellular pertussis vaccines utilized in Australia since the late 1990s and early 2000 [11]. Importantly, prn2–ptxP3 isolates (83% of the total isolates) may demonstrate both increased virulence and the ability to evade acellular pertussis vaccine-induced protection [11]. Other studies in Australia, the Netherlands and Finland also demonstrate increasing genetic diversity away from non-acellular pertussis vaccine antigens, suggesting vaccine selective pressure toward "non-vaccine" strains of *B. pertussis* [12–14], and of selection for strains with a novel allele in the pertussis toxin promoter gene resulting in increased production of pertussis toxin (Ptx) and disease of increased severity [12,15,16].

Whether such genetic changes have, in fact, led to increased pertussis susceptibility and subsequent outbreaks remains unclear. More data, particularly over longer time periods, are needed on this particular issue, and it raises the specter of vaccines as potential mutational pressure agents driving selection of vaccine-resistant organisms. To more clearly identify such a possibility, long-term studies spanning decades are needed in order to identify the development of vaccine-resistant organisms specific to vaccine antigens. Such studies are urgently needed, though are unlikely to be funded as the time period involved is beyond normal human and funding agency interest, and would require decades to fully define and investigate.

4. Inadequate and confusing vaccine recommendations

Readers may recall that whole cell pertussis vaccines were used exclusively in the U.S. until 1997 when acellular pertussis vaccines were recommended for the entire childhood series of immunizations. It was not until 2006 that a recommendation for the use of Tdap for U.S. adolescents and adults was made. This was followed by recommendations for a "cocooning strategy" that on the surface seemed rational – immunize those who come into contact with, and could expose, infants and young children at risk or too young to receive pertussis vaccine. Among adults, it was recommended that Tdap be substituted for one of the decennial Td boosters, then modified to recommend that at least 2 years elapse since the last Td before administering Tdap, then further modified to eliminate any required time interval between Td and Tdap in adults. Additionally, the vaccine was initially recommended only for persons up to age 65, and more recently amended to eliminate any upper age restriction. Finally, recent guidelines now include recommendations to administer Tdap to pregnant women after 20 weeks of gestation. Such a rapid cascade of recommendations resulted in neither patient nor practitioner being able to keep track of the confusing panoply of changing recommendations, which, predictably, resulted in inadequate population vaccine coverage and widespread uncertainty regarding appropriate use of the vaccine. As a result, many patients and providers simply deferred using the vaccine out of ignorance or uncertainty.

5. Summary

Control/elimination of pertussis in the U.S. has not failed for lack of effort. The current U.S. schedule for pertussis immunization is time-consuming and includes DTaP at 2, 4, 6, and 15–18 months of age, another dose at 4–6 years of age, followed by an adolescent booster (Tdap) at 11–12 years of age – a total of six doses of vaccine; resulting in short-term – but not long-term – immunity, and a continued modification of vaccine recommendations as noted above. Given this onerous schedule, high rates of vaccine coverage, and yet continuing endemicity and sustained outbreaks, it is apparent that multiple strategies are important going forward if we are to control or eliminate pertussis:

1. More research into the determinants of protective long-term durable immunity to *B. pertussis*.
2. Long-term studies of the possible selective mutational pressure of acellular pertussis vaccines on newly emerging *B. pertussis* strains.
3. Basic and clinical immunology research on the long-term effects of Th1 vs. Th2 immune response skewing by different pertussis antigen components and vaccine formulations in infants.
4. Research to guide new adolescent and adult recommendations to administer the current Tdap vaccine on a more frequent basis (given the issues of waning immunity), with strong consideration toward the use on a decennial basis. Limited information suggests this to be safe – but efficacy studies are needed to know if this is often enough [17].
5. Development of a more immunogenic and efficacious pertussis vaccine that requires far fewer doses and induces long-term durable protective immunity.

No one should be satisfied with the current state of affairs. Current licensed vaccines, while safe and with relatively good short-term protective immunity, nonetheless appear to require intermittent boosting. In combination with anti-vaccine sentiment, our general inability to administer this many doses of any vaccine to any group, the high cost, and the generally poor track record of physicians (especially physicians who care for adults) to accurately diagnose pertussis infections is reason for a new way forward. Pertussis is not just a childhood disease, immunity after vaccine or disease is not life-long, morbidity and mortality from disease is considerable, and sustained large-scale outbreaks are apparent. Academic researchers, vaccine manufacturers, and public funding entities (NIH, CDC, others) must galvanize around the goal of producing a safe and more effective vaccine with long-term immunity and a method to provide such a vaccine universally. The alternative is the crisis we now find ourselves collectively in, and the continued morbidity and mortality of this infection in the population.

Disclosures

Dr. Poland has offered consultative advice on novel non-Tdap vaccines to Merck & Co. Inc., Novartis Vaccines and Therapeutics, and Sanofi Pasteur.

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