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INVITED REVIEW

The 112-Year Odyssey of Pertussis and Pertussis Vaccines—Mistakes Made and Implications for the Future

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Effective diphtheria, tetanus toxoids, whole-cell pertussis (DTwP) vaccines became available in the 1930s, and they were put into routine use in the United States in the 1940s. Their use reduced the average rate of reported pertussis cases from 157 in 100 000 in the prevaccine era to <1 in 100 000 in the 1970s. Because of alleged reactions (encephalopathy and death), several countries discontinued (Sweden) or markedly decreased (United Kingdom, Germany, Japan) use of the vaccine. During the 20th century, *Bordetella pertussis* was studied extensively in animal model systems, and many "toxins" and protective antigens were described. A leader in *B pertussis* research was Margaret Pittman of the National Institutes of Health/US Food and Drug Administration. She published 2 articles suggesting that pertussis was a pertussis toxin (PT)-mediated disease. Dr Pittman's views led to the idea that less-reactogenic acellular vaccines could be produced. The first diphtheria, tetanus, pertussis (DTaP) vaccines were developed in Japan and put into routine use there. Afterward, DTaP vaccines were developed in the Western world, and definitive efficacy trials were carried out in the 1990s. These vaccines were all less reactogenic than DTwP vaccines, and despite the fact that their efficacy was less than that of DTwP vaccines, they were approved in the United States and many other countries. DTaP vaccines replaced DTwP vaccines in the United States in 1997. In the last 13 years, major pertussis epidemics have occurred in the United States, and numerous studies have shown the deficiencies of DTaP vaccines, including the small number of antigens that the vaccines contain and the type of cellular immune response that they elicit. The type of cellular response a predominantly, T2 response results in less efficacy and shorter duration of protection. Because of the small number of antigens (3–5 in DTaP vaccines vs >3000 in DTwP vaccines), linked-epitope suppression occurs. Because of linked-epitope suppression, all children who were primed by DTaP vaccines will be more susceptible to pertussis throughout their lifetimes, and there is no easy way to decrease this increased lifetime susceptibility.

Keywords. cellular response; DTaP; DTwP; linked-epitope suppression.

During the 20th century, *Bordetella pertussis* was studied extensively in mice, and many toxins and "protective antigens" were described [1, 2]. A leader in pertussis research was Margaret Pittman, who worked at the National Institutes of Health/US Food and Drug Administration (FDA) from 1936 to 1990. She suggested that pertussis was a pertussis toxin (PT)-mediated disease [3, 4]. Because contemporary diphtheria, tetanus toxoids, whole-cell pertussis (DTwP) vaccines were associated with significant adverse effects, Dr Pittman's views led to the idea that less-reactogenic acellular diphtheria, tetanus, pertussis (DTaP) vaccines could be produced.

Yuji Sato, who was trained at the National Institutes of Health/FDA and was influenced by Dr Pittman, returned to Japan and developed the first acellular pertussis (aP) vaccines [5]. Dr Sato's goal was to produce a PT toxoid vaccine, but his vaccines also contained filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae 2 (FIM-2). In the 1980s, many aP vaccines were developed, and in the 1990s, definitive efficacy trials with many aP and diphtheria, tetanus, acellular pertussis (DTaP) vaccines were carried out in Europe and Africa [1, 2, 6–20].

Despite the fact that in all but 2 of the efficacy trials the DTwP vaccines had greater efficacy than did the DTaP vaccines being studied, DTaP vaccines were licensed and used in many countries throughout the world; DTaP vaccines had replaced DTwP vaccines. The urgency to adopt DTaP vaccines was driven largely by antivaccine activist groups such as "Dissatisfied Parents Together." During the rush to adopt DTaP vaccines and tetanus, diphtheria, acellular pertussis vaccines for adults (Tdap), much of the history relating to human pertussis was overlooked [1, 2, 21–23].

Since 1997, the DTaP vaccination policy has created a cohort of people (the number of which is expanding yearly) who are more susceptible to repeated clinical illness with *B pertussis* infection than are DTwP-vaccinated children. There is no feasible way to make this cohort less susceptible.

In this review, I address the epidemiology of and facts, fiction, myths, and misconceptions related to human pertussis and suggest an approach for the future.

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EPIDEMIOLOGY

The epidemiology of reported pertussis is different from that of *B pertussis* infection and illness [24]. In 2012, in the United States, 48 277 cases of pertussis were reported. This was the greatest number of reported cases since 1955. Approximately 35 years ago, the number of cases and rates of reported pertussis started to climb and marked peaks occurred in 2005, 2010, 2012, and 2014 (Figure 1).

Reported Pertussis in the United States

In the prevaccine era, reported pertussis had cyclic peaks every 2 to 5 years [1, 2, 24–26]. Pertussis immunization reduced the average rate of reported pertussis from 157 per 1 000 000 to <1 per 1 000 000 [25]. In the pertussis vaccine era (both whole-cell and acellular vaccines), the cyclic peaks of reported pertussis have been the same as those in the prevaccine era. Because the cycles of pertussis are the same today as they were in the prevaccine era, we know that *B pertussis* is circulating today in a manner similar to that in the prevaccine era [1, 2, 26–29]. Numerous studies since 2004 have noted that pertussis in adults is common and the major source for infections in infants [1, 2, 7, 30–40].

In the past, virtually all cases of pertussis in adults were misdiagnosed [37]. They were thought to be cough-variant asthma, gastrointestinal reflux, or a respiratory viral infection. In a similar vein, pertussis in infants also has been misdiagnosed as respiratory viral illness [25, 35].

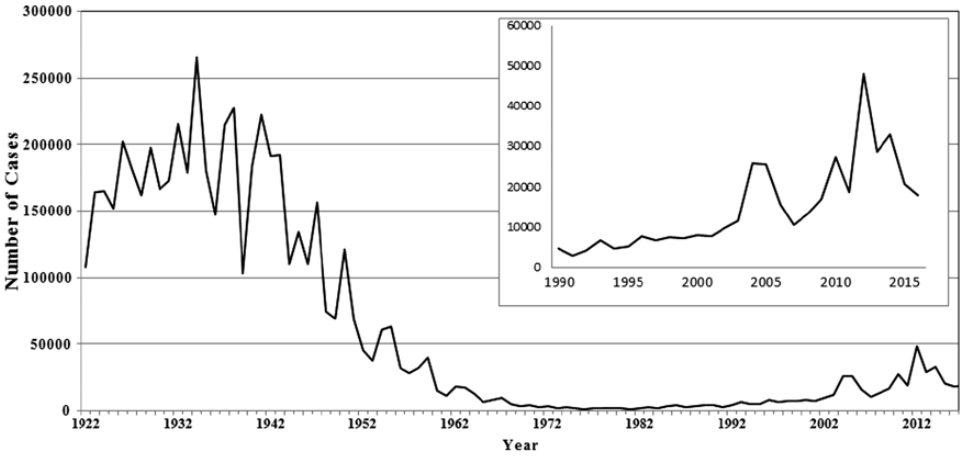
A number of reasons exist for the reemergence of reported pertussis in the beginning of the 21st century. As noted in the introduction, DTaP vaccines are less effective than DTwP vaccines (discussed in depth later in this review). However, the resurgence started approximately 15 years before the switch from DTwP to DTaP vaccines. Therefore, it is my opinion that the main reason for the initial resurgence was greater awareness of pertussis. Greater awareness occurred because much media attention was paid to true and perceived DTwP reactions, the number of pertussis articles in the literature related to vaccine reactions increased, many phase 2 DTaP vaccine studies were carried out, and, in the 1990s, the definitive vaccine-efficiency trials were performed. Also, in my opinion the of the polymerase chain reaction assay for diagnosis around 2005 also contributed to the resurgence in pertussis reports. In addition, single-serum serologic diagnosis for adolescent and adult pertussis became available.

Bordetella pertussis Infection

In the late 1980s through 2008, studies on *B pertussis* infection were performed in 3 ways: (1) the percentage of prolonged cough illnesses in adolescents and adults caused by *B pertussis* infection; (2) the rates of *B pertussis* infection in adolescents and adults; and (3) the rates of *B pertussis* cough illnesses in adolescents and adults.

Between 1983 and 1999, 13 studies on the percentage of prolonged cough illness in adolescents and adults attributable to *B pertussis* infection were published [24]. In the majority of these studies, the diagnosis was made by finding a significant rise in titer or finding a high titer to PT, FHA, PRN, FIM, in an enzyme-linked immunosorbent assay or by agglutination. The positive rates varied from 12% to 52% (median, 26%).

However, because only the antibody to PT is specific for *B pertussis* infection, these rates include illnesses attributable to other *Bordetella* spp, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* [41]. In 7 studies, it was possible to find only cases determined by immunoglobulin A (IgA) or IgG antibody titer increases, high PT titers, or culture or a



Source: 1922-1949 passive reports to the Public Health Service. 1950 to 2017 Centers for Disease Control and Prevention (CDC) yearly National Notifiable Diseases Surveillance System reports.

Figure 1. Reported pertussis cases, 1922–2016.

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polymerase chain reaction assay positivity. Here, the rates varied from 7% to 17% (median, 13%). Our group performed the first of these studies in UCLA students between 1986 and 1989.

An interesting aspect of all the studies is that *B pertussis* illnesses occurred throughout the year. Therefore, these data suggest that pertussis is endemic in adolescents and adults.

Seven published studies contain data relating to the yearly rate of *B pertussis* infections. In 6 of these studies, the rates were determined by finding significant titer increases between 2 time points. In the other study, the infection rates were determined by the PT antibody value being above the cutoff limit [41]. The quality of the data varied considerably between the studies. Our group performed the first of these studies [42], in which we obtained yearly serum samples from the same subjects over a 5-year period. The yearly rate was a surprising 6%. In 2 studies in which the rates were determined between only 2 time periods, the yearly rates were 1% to 2.2%.

In Cleveland, Ohio, we collected serum samples every 4 months for 3 years from a group of 100 adults aged ≥65 years who were living in the community [43]. In this group, the yearly rate was 3%. Results from a de Melker et al [44] study supported found in our 2 previous studies [42, 43]. Specifically, the yearly rates in the ≥65-year age group of 3% and the rate of 6% in our study in which we obtained sera from the same subjects over a 5-year period matched those noted by de Melker at al..

Two studies in which the authors determined the rates of *B pertussis* cough illness in adolescents and adults have been performed. The first was a Centers for Disease Control and Prevention study in participating doctors' offices in Minneapolis and St Paul, Minnesota [45]. In that study, the annual rate was 500 per 100 000. The second of these studies involved approximately 1400 persons who were controls in a vaccine efficacy trial in adolescents and adults. In that study, the annual rate was 370 per 100 000 [46]. In both of these 2 studies, there existed considerable "observer bias" [47], a term that our group in Erlangen, Germany, coined. Specifically, if one has a preconceived idea of what pertussis is, then one will overlook less-severe cases. Observer bias was clearly a significant problem in the Minnesota study. The authors actually studied only approximately 5% of those who met study-entry criteria; mild illness was clearly overlooked. In our UCLA study, observer bias was also a problem, because the study nurses tended to ignore the mild cases, although they met the study criteria.

Immunity After *B pertussis* Infection and DTwP Vaccination

A common belief is that *B pertussis* infection results in lifelong immunity and that DTwP vaccine immunity is relatively short lived [48]. While working in Germany in the 1990s, I saw many cases of pertussis in adults [49]. It was assumed that most of these illnesses occurred in adults who had been primed initially by *B pertussis* infection in childhood. Our group previously studied pertussis in UCLA students [50], and it was assumed then that most of these students were primed initially by DTwP vaccine. My impression and the results of an analysis of data from 2 of our published studies suggest that the illness in the previously disease-primed German participants was generally more severe than the illness in the American students who were primed initially with DTwP vaccine. Using sera from 21-year-old German adults and 21-year-old students in the United States, we examined IgG and IgA antibodies to agglutinogens, FIM-2, FHA, PRN, and PT [51]. It should be noted that IgA antibody occurs only after infection and not after DTwP vaccination. Because pertussis was an epidemic in Germany at the time of this study and was not being observed in adults in the United States, one would expect the IgG and IgA titers to be higher in the Germans than in the Americans. However, such was not the case. The IgG titers to all 5 antigens were significantly higher in the Americans, whereas the IgA titers were similar in the German and American participants.

The IgG findings suggest that DTwP vaccination provides better protection than natural infection. The IgA data indicate that *B pertussis* was circulating in both countries in similar fashions despite the fact that recognized pertussis was an epidemic in Germany and was not being observed in the United States.

In reviewing publications from the 1920s, 1930s, and 1940s, it is clear that repeat illness caused by *B pertussis* was not uncommon and that pertussis in adults was overlooked [52–58].

A summary of reported pertussis cases is presented in Table 1.

WHOLE-CELL VACCINE ERA

History of DTwP Vaccines

As noted in the introduction, the universal use of DTwP vaccines, which started in the late 1940s, led to a 157-fold reduction in the incidence of reported pertussis. *B pertussis* was isolated in 1906 [59], and because pertussis was frequently fatal at the time, attempts were made to make vaccines for treatment and protection [4, 21, 25, 26, 36, 53–55]. In 1923–1924 in Denmark, Madsen [55] showed some protection from vaccination. In the 1930s, many candidate vaccines were developed, and in 1944, pertussis immunization was endorsed by the American Academy of Pediatrics [26].

Table 1. Summary of Reported Pertussis Cases in the Prevaccine and Vaccine Eras

1. *B pertussis* infections in adolescents and adults are very common and endemic in the current vaccine era
2. Data from Germany in the early 1990s, when few children were being immunized and pertussis was epidemic, and early observations in the United States suggest that infections in adolescents and adults were also common and endemic in the prevaccine era
3. Rates of reported pertussis are 40- to 160-fold less common than actual illness rates
4. Asymptomatic infection is 4–22 times more common than symptomatic infection
5. Symptomatic adolescents and adults currently are the major source of infection in unvaccinated children

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In the 1930s, it was realized that good antibody response and clinical protection after immunization depended on the number of killed organisms in the vaccine, and because of reactions (toxicity), the number of organisms that could be given in a single dose was limited. As far back as the 1940s, study reports have suggested that vaccines cause severe neurological disease (vaccine encephalopathy) [60–62]. One of these studies, form London in 1974, led to a drastic decrease in DTwP vaccine use and severe epidemic disease 3 years later [62]. Population-based studies in Sweden, England, and Wales found very high rates for vaccine encephalopathy [63, 64]. The concern regarding vaccine encephalopathy led to discontinuation of DTwP vaccine use in Sweden and Japan. In the United States, vaccine use remained relatively stable, but an epidemic of pertussis vaccine lawsuits spread in the 1980s and led to the National Childhood Vaccine Injury Act of 1986 [65]. This act provided persons allegedly injured by a routine childhood immunization a no-fault alternative to litigation via the traditional tort system.

The results of a number of controlled studies between 1979 and 2004 indicated that no risk of severe neurologic disease after DTwP vaccinations existed [66–76]. It was noted by myself and Shields [77] (a pediatric neurologist) that what was being called pertussis vaccine encephalopathy was not an encephalitis-like event but, instead, the first seizure or seizures of infantile epilepsy.

Sudden infant death syndrome (SIDS) was also thought to be a complication of DTwP vaccination. However, the peak age of SIDS occurrence is approximately 10 weeks, and because the first DTwP dose in the United States was administered at approximately 8 weeks of age, the temporal association between SIDS and vaccination would be expected. In the late 1970s and 1980s, considerable media coverage inferred a cause-and-effect relationship. Controlled studies in 1987 [78] and 1988 [79] found no causal relationship between DTwP immunization and SIDS. SIDS is now known to be a result, in large part, of the prone sleeping position.

B. PERTUSSIS, THE ORGANISM AND ITS PATHOGENESIS

In bacterial infections, there are usually 4 steps in pathogenesis, (1) entry into the host and attachment, (2) evasion or disruption of host defenses, (3) development of local damage, and (4) establishment of systemic disease by virtue of dissemination of organisms or their products. In 1940, William H. Holmes [22] wrote a book on bacillary and rickettsial infections, and the pertussis chapter is of considerable interest. He made the following 5 important observations: (1) unlike other diseases such as polio or measles, pertussis has no ancient history, (2) pertussis results in no characteristic changes such as rash or meningitis, (3) the paroxysmal cough is distinctive, but its cause was elusive, (4) pertussis kills more female than male infants, and (5) although it is an infectious disease, there is no fever during the spasmodic stage and no physical findings.

Pathology

In 1912, F. B. Mallory and A. A. Hornor published an article on histological lesions in the respiratory tract of patients with pertussis [23]. They studied the respiratory tract of 3 children who died as a result of pertussis. All 3 of these children had a rather protracted course with secondary infection; nevertheless, the authors noted areas of normal ciliated cells in the trachea, bronchi, and bronchioles. The ciliated cells had coccobacilli attached to the cilia. In 2008, Paddock, Sanden, and I [80] reported the pulmonary pathology of 15 infants who died as a result of pertussis. From this study we proposed a mechanism for death in young infants. Our hypothesis was that the leukocytosis with lymphocytosis caused aggregates of cells in the arterioles, which resulted in irreversible pulmonary hypertension. The results of studies by our extended California group of investigators support that hypothesis [36, 40, 80–86]. We have found that the degree of leukocytosis with lymphocytosis and the rapidity of the increase in white blood cell count relate to the occurrence of irreversible pulmonary hypertension and death. It also should be noted that this process is noninflammatory [81]. The aggregates are made up of mature neutrophils and lymphocytes that reflect the cells circulating in the blood. The immune response in the lung is an influx of intra-alveolar macrophages; young neutrophils (band forms) are not seen.

Perhaps more important is that we duplicated the findings of Mallory and Hornor [23] from almost 100 years ago. We noted normal ciliated cells with *B pertussis* cells attached to the cilia.

If we now go back and look at the steps in pathogenesis for *B pertussis*, we note that local damage does not occur (unless there is a secondary bacterial or viral infection) and that there is no systemic disease.

CLINICAL PERTUSSIS

Clinical pertussis is a toxin-mediated disease caused by PT, which inhibits host cell G proteins, and a second yet-unidentified toxin that causes a unique cough [2, 40]. There is no inflammatory process unless a secondary infection is present. PT causes leukocytosis with lymphocytosis, which leads to pulmonary hypertension, shock, and organ failure in young infants [80–86]. After primary exposure to PT by illness or immunization, the clinical manifestations of PT (leukocytosis with lymphocytosis) never recur with subsequent infection, presumably because of the rapid antibody response.

The illness manifestations in persons who have previously responded to PT are attributable solely to the yet-unidentified "cough toxin." Because persons of all ages experience cough with *B pertussis* infection, it would seem that either this toxin is poorly immunogenic or immunity to it wanes rapidly.

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Infection by *B pertussis* is facilitated by a number of proteins. These proteins either facilitate attachment (FIM-2/3) or disrupt the innate immune responses.

Since 1909, numerous *B pertussis* toxins have been identified in studies in mice. However, 2 of these toxins (dermonecrotic toxins and tracheal cytotoxin) probably play no significant role in human infection [2].

aP VACCINES

As noted in the introduction, aP and DTaP vaccines were developed in the 1980s and were tested extensively in the 1990s. These vaccines contain between 1 and 5 antigens, in contrast to DTwP vaccines, which contain more than 3000 *B pertussis* antigens. All DTaP vaccines are less reactogenic than are DTwP vaccines because they contain virtually no lipopolysaccharide (LPS).

Four Reasons Why DTaP Vaccines Are Inferior to DTwP Vaccines

There are 4 reasons why DTaP vaccines are inferior to DTwP vaccines, (1) genetic changes in *B pertussis* have contributed to increased susceptibility, (2) the Th17/Th1 cellular immune response after DTwP vaccination is more effective than the T-helper (Th2) response after DTaP vaccination, (3) DTaP vaccines have a suboptimal balance of antigens, and (4) linked-epitope suppression [2, 40, 87–97].

Genetic Changes in *B pertussis*

Genetic changes that contribute to increased susceptibility to *B pertussis* did not occur in the DTwP era. The total number of protective antigens in DTwP vaccines is not known, but it is likely that more than 20 of them exist. In contrast, DTaP vaccines contain at most 5 proteins. Recent changes in *B pertussis* in the acellular vaccine era include the following: (1) a change from the ptx P1 to the ptx P3 allele, (2) the development of PRN-deficient mutants, and (3) an increase in FIM-3B strains. Of these 3 genetic changes, only the occurrence of PRN-deficient mutants is important. In the United States, the majority of circulating *B pertussis* strains are currently PRN deficient. Because antibody to PRN is most important in protection [93, 94], the circulation of these strains should contribute to DTaP and Tdap vaccine failures. At present no evidence for such failures exists; the antibody to the B subunit of PT provides considerable effectiveness against "typical pertussis." We know this because in Denmark, a PT toxoid vaccine has been used for 20 years, and it has controlled severe pertussis. Therefore, to show that PRN-deficient mutants are contributing to DTaP and Tdap vaccine failures, a search for *B pertussis* infections in patients with less-severe afebrile cough illness would be necessary.

Type of T-Cell Immune Response

Information from studies in baboons have yielded valuable information related to T-cell immune responses [87–89]. After infection or DTwP vaccination, a specific Th17 and Th1 memory response is elicited, whereas after DTaP immunization, a Th1/Th2 response is elicited. The Th17/Th1 response prevents infection and disease and also provides longer-lasting protection than does the Th1/Th2 response.

Incorrect Balances of Antigens in DTaP Vaccines

In 2 of the vaccine-efficacy trials of the 1990s, the investigators carried out their studies in ways that enabled the determination of serologic correlates of protection [93, 94]. In both studies it was noted that antibody to PRN or FIM led to an effectiveness of approximately 70%. It was noted also in both studies that higher levels of antibody to PT diminished the effectiveness of antibody to FIM. In the Swedish study (but not in the German study), evidence that high levels of antibody to PT diminished the effectiveness of antibody to PRN was also found (unpublished data of Storsaeter J, Hallander HO, Gustafsson L, Olin P).

Linked-Epitope Suppression

In a study of adenylate cyclase toxin (ACT), the authors noted that children with a primary *B pertussis* infection had a vigorous antibody response to ACT [95]. In contrast, the antibody response to ACT in those whose DTaP vaccine failed was blunted. At that time, The authors suggested that this was similar to "original antigenic sin" in influenza. The concept of original antigenic sin in influenza was suggested more than 60 years ago. The immunologic memory of children is such that with a second influenza A infection, the major antibody response is directed at the strain with which they were infected originally and not to the new infecting strain. Using sera from 2 vaccine trials in Sweden, we noted that individuals who were not protected by a PT toxoid vaccine did not develop antibody to FHA, and those for whom a PT/FHA vaccine failed did not develop antibody to either PRN or FIM [96]. In "linked-epitope suppression," memory B cells out-compete naive B cells for access to the *Bordetella* epitopes because they are more numerous and their receptors exhibit a higher antigen affinity. Linked-epitope suppression applies as the immune response to novel epitopes is suppressed by the strong response to initial components if they are introduced together.

A study in Australia by Sheridan et al [97] showed the practical importance of linked-epitope suppression. They examined pertussis attack rates in 40 891 children in Queensland between 1999 and 2011. In those children who were initially primed by DTwP vaccine, the average annual attack rate was 5.2% (95% confidence interval, 2.7%–9.1%); in contrast, the average annual attack rate in those primed by DTaP was 13.2% (95% confidence interval, 7.0%–22.6%). Even though the priming with DTwP vaccine was further back in time, the annual attack rate was significantly lower in these participants than in those who were primed with DTaP.

The finding of initial priming by DTwP vaccine leading to greater efficiency than priming by DTaP vaccine is explained by linked-epitope suppression caused by the preferential responses

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of memory B cells after secondary exposure to vaccine components. DTwP vaccines contain >3000 proteins. Antibody to many of these proteins contribute to protection. DTaP vaccines contain up to only 5 proteins.

Recent Tdap Studies in Adolescents Who Were Primed by DTaP Vaccines

Three studies on Tdap vaccine effectiveness have been performed in the United States. The vaccine-effectiveness rates during the first year were 75.3%, 73.0%, and 68.8%. However, after 3 years, almost no evidence of effectiveness was found [98–100].

WHAT SHOULD BE DONE TO AMELIORATE THE DTAP COHORT

We should be more vigilant than we have been in the past to recognize and treat pertussis in all age groups so that transmission to young infants is reduced. Most important (although not discussed in this review) is to ensure that all pregnant women receive the Tdap vaccine between 27 and 36 weeks' gestation with each pregnancy. Also, we should consider routinely administering Tdap vaccine every 3 years to all adolescents and adults who were primed with a DTaP vaccine. This suggestion is contrary to that in the current Advisory Committee on Immunization Practices recommendations. However, from the data available [98–100], this approach could be expected to decrease the circulation of *B pertussis* in adolescents and adults. Also, Tdap should be administered to all adolescent and adults exposed to *B pertussis* during a school or other group outbreak.

NEW PERTUSSIS VACCINES TO PREVENT OUR CURRENT PROBLEM

New DTaP Vaccines

From the data discussed and presented in this report, it is my opinion that a new DTaP vaccine is not a viable option. It would seem that getting the correct number and balance of antigens would be close to impossible.

Live Vaccines

In Lille, France, Locht et al [101–104] developed an extremely promising live vaccine that seems to be both safe and effective. This candidate live vaccine, which is delivered intranasally, was developed by Locht et al approximately 12 years ago [103]. The vaccine, BPZE1, was attenuated by the removal of dermonecrotic toxin, the reduction of tracheal cytotoxin to a background level, and the complete inactivation of PT [104]. Trials with this vaccine are expected to begin in the United States soon.

DTwP Vaccines That Are Less Reactogenic

In a UCLA–FDA project, vaccine reactions related to 15 752 immunizations with DTwP vaccine were studied in California between January 1, 1978, and December 15, 1979 [105]. In a substudy, reactogenicity according to vaccine lot, endotoxin content, pertussis vaccine potency, and the percentage of weight gain in mice was analyzed [106]. From this study and many others in the 1980s, it was realized that the main cause of reaction after DTwP vaccination in infants was LPS (endotoxin) [1].

After the general recognition that LPS in DTwP vaccines was the major cause of vaccine reactions, attempts were made to detoxify vaccines. In 1974, Cooperstock [107] found that endotoxin could be inactivated by polymyxin B. Studies by Bannatyne et al [108, 109] found that exposure of DTwP vaccines to polymyxin B decreased endotoxin activity, as assessed in a limulus-lysate test. This treatment did not decrease the protective effect of the vaccine in a mouse-protection test [108].

More recently, at the Institute Butantan in São Paulo, Brazil, a DTwP vaccine from which the LPS had been removed by chemical extraction was produced [110, 111].

The immunization of children with DTwP vaccine results in specific LPS antibody responses [1, 26, 112]. Studies in animals found that LPS is an agglutinogen. Therefore, antibody to LPS will be an anti-adhesin. Antibody to LPS has complement-dependent bactericidal activity. It has been noted also that LPS is a potent adjuvant. From these facts, it would seem that the removal of LPS from DTwP vaccines is not a good approach.

The technology is available to modify LPS (lipid A) so that its beneficial effects are retained but its reactogenicity is eliminated [113–118]. Fernandez and I are presently discussing this DTwP vaccine approach with a vaccine company.

SUMMARY

The use of animal model systems (specifically those with mice) led to many mistakes that led the way to our present DTaP problems. Countries that currently use DTwP vaccines should continue to do so. We should increase our awareness of pertussis in adults, because they are the reservoir for the continued circulation of *B pertussis* and the source of infections in young infants. Future cohorts would benefit from the development and use of live vaccines and less-reactogenic DTwP vaccines.

Note

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