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Why Do Pertussis Vaccines Fail?

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During the 2010 pertussis epidemic in California, there was considerable concern in the press and in public health communications about the possible contribution of vaccine failures to the problem.[1,2] In this commentary, I examine why pertussis vaccines fail and Table 1 lists 8 possible reasons.

The first reason, and perhaps the most important one, is that our estimates of vaccine efficacy have been inflated because of case definition.[3–11] At the time of the pediatric diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine efficacy trials in the early 1990s, it was hoped that a universal case definition could be developed so that the results of the various trials could be compared. To this end, the World Health Organization (WHO) case definition was developed.[3] The primary case definition required laboratory confirmation and ≥21 days of paroxysmal cough. I was a member of the WHO committee and disagreed with the primary case definition because it was clear at that time that this definition would eliminate a substantial number of cases and therefore inflate reported efficacy values.[4–11] Nevertheless, the Center for Biologics Evaluation and Research of the Food and Drug Administration accepted this definition, and package inserts of the US-licensed DTaP vaccines reflect this. For example, Infanrix (containing 25 μg pertussis toxin [PT], 25 μg filamentous hemagglutinin [FHA], and 8 μg pertactin [PRN]) and Daptacel (containing 10 μg PT, 5 μg FHA, 5 μg fimbriae [FIM]-2/3, and 3 μg PRN) have stated efficacies of 84% and 85% respectively. When less severe cough illness is included, however, the efficacies of these 2 vaccines decrease to 71% and 78% respectively.[10,11]

In addition, even these latter efficacies are likely inflated owing to investigator or parental compliance with the study protocol (observer bias). For example, in the trial in Germany, Acell-immune (containing 34.4 μg FHA, 3.2 μg PT, 1.6 μg PRN, and 0.8 μg FIM-2) had a WHO efficacy (≥21 days of paroxysmal cough) of 83%, and an efficacy of 72% when cough illness of ≥7 days was included.[12] In this trial, the investigators were to call the parents of study participants every 2 weeks and then evaluate every child with a cough of >7 days. During the study, it became apparent that only about one-third of the investigators were following the protocol. In the subset of study patients followed by the compliant investigators (who worked up mild illnesses as well as "typical pertussis"), the DTaP vaccine efficacy was only 40%.

It is very likely that observer bias also occurred in the 2 double-blinded trials in Sweden and Italy,[10,11] because the study nurses called the families only every month (Italy) or every 6 to 8 weeks (Sweden). Therefore, in both studies the parents were the primary observers. Because typical pertussis was more likely in diphtheria and tetanus toxoids recipients than in DTaP recipients, and because the parents "knew pertussis" (it was epidemic in both countries), they would be more likely to have their children evaluated if the illness was typical. This would inflate efficacy.

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ABBREVIATIONS

DTaP—pediatric diphtheria and tetanus toxoids and acellular pertussis vaccine
DTP—pediatric diphtheria and tetanus toxoids and whole-cell pertussis vaccine
FHA—filamentous hemagglutinin
FIM—fimbriae
PCR—polymerase chain reaction
PRN—pertactin
PT—pertussis toxin
WHO—World Health Organization

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TABLE 1 Possible Reasons Why DTP, DTaP, and Adolescent- and Adult-Formulated Tetanus and Diphtheria Toxoids and Acellular Pertussis Vaccines Fail

1. Overexpectation of efficacy because of case definition.
2. Inflated estimates of efficacy because of observer bias.
3. Other *Bordetella* sp are the cause of similar cough illnesses.
4. Lack of initial potency.
5. Decay in antibody over time.
6. Incomplete antigen package.
7. Incorrect balance of antigens in the vaccine.
8. Genetic changes in *B pertussis*.

Until the widespread use of polymerase chain reaction (PCR) for the diagnosis of pertussis, the role of *Bordetella parapertussis* in pertussis in the United States was thought to be minimal.[13] Today, however, the use of dual primers designed to amplify bp segments of IS481 and of IS1001 in real-time PCR systems has proven to be a sensitive method of identifying *B parapertussis* infections (IS1001 positives). Of nasopharyngeal specimens from patients with cough illnesses sent to a commercial laboratory for PCR testing, during the 3-year period 2008–2010, it was found that 14% of the positive specimens were IS1001 positive, indicating *B parapertussis* infection.[14] In 2010, the positivity rate was 16.5%. These cases would appear as vaccine failures when they are not, as protection against *B parapertussis* is not expected from current pertussis vaccines.

Lack of initial vaccine potency was a problem with at least 1 lot of a US pediatric diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine, but this is not a problem with presently in use DTaP or adolescent- and adult-formulated tetanus and diphtheria toxoids and acellular pertussis vaccines. Individual vaccinees do not initially respond to all vaccine antigens after immunization, however.[15] Decay in antibody to specific vaccine proteins over time is, of course, well known; however, its extent has been overlooked. For example, in a recent study between the third and fourth doses, antibody to PT, FHA, PRN, and FIM 2/3 fell eightfold, sixfold, sixfold, and sevenfold respectively.[16] In the same study, the fall of antibody to the same proteins (PT, FHA, PRN, and FIM 2/3) between the fourth and fifth doses was 17-fold, 14-fold, 10-fold, and 16-fold respectively. The fall off of antibodies after the fifth dose has not been examined; however, 2010 California data show that between age 5 and 10 the percentage of vaccine failures per total cases increases linearly each year.[17]

Vaccines that contain 3 or more antigens have better efficacy than 1- or 2-component vaccines.[13] At the present time, the primary vaccines in use in the United States are 3- and 5-component vaccines, so that incomplete antigen package is not presently a major problem. A head-to-head comparison of a 3- versus a 5-component vaccine indicated that the 5-component vaccine had greater efficacy, however.[18]

The last 2 items in Table 1 are less clear cut. Presently, there are data available that suggest that high values of antibody to PT in the presence of high antibody values to PRN or to FIM may have a blocking effect, resulting in decreased efficacy.[19–21]

Vaccine use has resulted in genetic changes in PT, PRN, and FIM in circulating *B pertussis* strains, and it has been suggested that this has led to increased vaccine failure rates.[22] At the present time, however, there is no evidence to support the hypothesis that evolution is allowing circulating *B pertussis* strains to escape from vaccine-produced antibodies.[23] If it were to occur, I would expect it to occur first in Denmark, where a PT toxoid vaccine has been in use for ~15 years; this, as yet apparently has not happened.

In summary, DTP vaccines generally have greater efficacy than DTaP vaccines. All vaccine efficacy has been inflated because of case definition and probably observer bias. In addition, other factors, as noted in Table 1, may contribute to the problem.

To overcome the problem, it needs to be recognized that *B pertussis* is circulating in all age groups and, therefore, for herd immunity there is a need to universally vaccinate all age groups at frequent intervals.[24] New vaccines should be considered for development that include changes to enhance efficacy but retaining a low reactogenicity profile. This could be DTaP vaccines with multiple additional components and perhaps containing less PT. An alternative would be to develop DTP vaccines with detoxified lipopolysaccharide (the cause of reactions to whole-cell vaccines). It has also been suggested to develop "live vaccines."[25] There are data available (not presented here), however, that indicate that immunity from DTP vaccines is better than that after infection; therefore, I do not think "live vaccines" are a worthwhile approach.

Clearly, additional investments and innovations in pertussis vaccine development are needed to remove pertussis from its position as the leading vaccine-preventable disease in the United States.

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