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Pertussis Vaccine:

A Critique

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Abstract

A critical level of serum IgG pertussis toxin antibody is both essential and sufficient to confer individual and herd immunity to pertussis. Monocomponent pertussis toxoid conferred such immunity in Sweden and in Denmark. We refute the notion that filamentous hemagglutinin, pertactin, and fimbriae add to the immunity conferred by pertussis toxoid and describe the artifact created when efficacy is estimated for multicomponent pertussis vaccines. Lastly, the genetically-inactivated mutant pertussis toxoid is safer, more immunogenic, and should be more effective than the current chemically-inactivated pertussis toxin.

Keywords

pertussis toxin; genetically-inactivated; monovalent; FHA; pertactin

In 1978 at an International Meeting on Pertussis, Margaret Pittman presented her theory that pertussis was a toxin-mediated disease.[1] Based upon Pittman's classic article, we proposed that a suitably inactivated and immunogenic pertussis toxoid is both essential and sufficient for a pertussis vaccine.[2,3]

The goal of having every child fully immunized against pertussis became closer to realization with the introduction of safer acellular pertussis vaccines in the 1990s. Despite a high vaccination rate, there has been an apparent resurgence of pertussis in the United States and other developed countries.[4,5] We were prompted to review this subject after a recent publication by the Word Health Organization on pertussis vaccine.[6] Remarkably, this document does not mention a potency assay or antibody level(s), or an explanation of how regulatory agencies could license pertussis vaccines with 1, 2, 3, or 5 components. We suggest that much of this confusion can be explained by the failure to recognize how serum IgG antitoxin could confer antibacterial immunity to pertussis. Insight into this problem can be provided by reviewing diphtheria vaccine.[7]

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SERUM IgG ANTITOXIN CONFERS ANTIBACTERIAL IMMUNITY TO DIPHTHERIA

Antitoxin does not lyse or opsonize *Clostridium diphtheriae*. Antitoxin protects phagocytic cells that can then opsonize and inactivate the pathogen. The protective effect of antitoxin, therefore, is indirect. There is no "protective" antitoxin level—there is only a correlation between antitoxin levels and immunity. Importantly, diphtheria toxoid induces both individual and "herd" immunity, and it is the latter that exerts the most important public health effect. The efficacy of diphtheria toxoid has never been measured by a doubled-blinded placebo-controlled trial. Diphtheria toxoid vaccine is only ~75% protective on an individual basis but is almost 100% protective against fatal diphtheria.[8] Diphtheria occurs in individuals with "protective" levels of antitoxin. At least one half of older children and adults in the United States do not have "protective levels" (≥0.01 U) of antitoxin.[9] Yet, there have been almost no cases of diphtheria in the United States or in other countries that vaccinate infants. *C. diphtheriae* tox+ is an inhabitant of and a pathogen for humans only. Current diphtheria toxoids are highly purified, can be considered as monocomponent vaccines, and probably elicit only antitoxin. Pappenheimer showed that when at least 50% of the population has "protective" levels of antitoxin, *C. diphtheriae* is reduced to nondetectable levels; it is this effect that is responsible for "herd" immunity.[10] It has been suggested that this situation is also valid for pertussis. "The suggestion of the possible elimination of the circulation of the organism (*Bordetella pertussis*) may seem farfetched to most people, but it should be recalled that the circulation of *C. diphtheriae*, as well as the control of diphtheria in much of the developed world, was brought about by immunizing both children and adults in the 1930s and 1940s."[11] The major reason for the persistence of pertussis, even in highly immunized populations, is that the cellular vaccine, used until the 1990s, was too toxic for adults and only diphtheria, tetanus (DT) vaccine was administered to adults.[12] As a result, older children and adults became susceptible to infection with *B. pertussis.* We predict that immunization of teenagers and adults with acellular pertussis vaccines will soon reduce the incidence of pertussis in all age groups.

MONOCOMPONENT PERTUSSIS TOXOID VACCINE CONFERS IMMUNITY TO PERTUSSIS

Two major double-blinded controlled studies and 1 comprehensive surveillance study showed that monocomponent pertussis toxoid confer immunity to pertussis. The first, a study in Stockholm, included a bivalent vaccine composed of pertussis toxoid and filamentous hemagglutinin (FHA) (JNIH-6) and a monocomponent pertussis toxoid (JNIH-7).[13] The control was the adsorbent alone. Two injections of these vaccines were administered 2 months apart to young children. The difficulty in diagnosing pertussis was not appreciated at that time and the initial report was confusing. Black-welder examined the data by actuarial analysis and showed that the JNIH-7 was at least as effective as JNIH-6.[14] The simultaneous administration of FHA with the toxoid had no positive effect. In a second study, Trollfors et al vaccinated 3-month-old children in Göteborg, Sweden, with 3 injections of a hydrogen peroxide–inactivated pertussis toxin, according to the Swedish recommended schedule.[15] The control was DT. According to the then newly devised diagnostic criteria of the World Health Organization (WHO),[16] the efficacy of the pertussis toxoid was 71% after 24 months of active surveillance after the third injection; similar results using nationwide surveillance were obtained by Danish workers, using the same vaccine.[17] Later, this pertussis toxoid vaccine was used to vaccinate all children in Göteborg born during the 1990s. This mass vaccination resulted in a significant reduction of both the number of isolates of *B. pertussis* and of hospital admissions for pertussis of adults and those too young to be fully immunized (herd immunity).[18]

ARTIFACT IN CALCULATING THE EFFICACY OF MULTICOMPONENT PERTUSSIS VACCINES USING THE CRITERIA OF THE WORLD HEALTH ORGANIZATION FOR DIAGNOSIS

Not commonly appreciated is that the efficacy of both cellular and acellular pertussis vaccines is only about 80%.[19] This is probably because of the fact that vaccine-induced antibodies do not kill *B. pertussis*. The protective effect of pertussis toxoid vaccination is indirect and similar to that of diphtheria–antitoxin protects pulmonary phagocytic cells against the inactivation exerted by pertussis toxin (PT).[20,21] Studies of vaccine efficacy have been complicated by the difficulty in diagnosing pertussis. *B. pertussis* is cultured readily during the early stages of disease when the coughing is not diagnostic. As the paroxysmal coughing appears, usually about 3 weeks after contact with a case, both the percent of positive cultures and the numbers of *B. pertussis* cultured decline.[22] When the disease becomes clinically manifest, the cultures are negative and the patients do not respond to antibiotics. The characteristic “whoop” and lymphocytosis occur mostly in infants and young children. Lastly, the efficacy of pertussis vaccines is related to the severity of the disease. To illustrate, when the criteria of whoops and more than 3 weeks of paroxysmal coughing are applied, the efficacy of cellular and acellular pertussis vaccines is approximately 90%.[23] When the criterion of 2 weeks of paroxysmal coughing is used, the efficacy of these vaccines may be as low as 60%. These factors are among the most important reasons why reports of the efficacy of pertussis vaccines are so varied.

Aside from the monocomponent pertussis toxoid studied in Göteborg and in Denmark, all other acellular pertussis vaccines contain FHA and pertactin and some also contain fimbriae.[24] In blinded and controlled studies, the efficacy of these multicomponent vaccines was estimated at approximately 84%.[14,24,25] But, these estimations are flawed because of an artifact created by the criteria of the WHO for diagnosis in vaccine efficacy trials.[16] The WHO requirements are ≥21 days of paroxysmal coughing and one of the following: a positive culture of *B. pertussis* or serological data indicating a statistically significant rise of PT or FHA antibodies (IgG). Another criterion, less used, is contact with a household case of pertussis. The artifact is caused by 2 factors: (1) isolation of *B. pertussis* from immunized patients is lower than from controls.[26–32] Accordingly, there is a greater reliance on the serologic diagnosis of pertussis in patients who have been vaccinated; (2) the percent of patients with a rise of antibodies to FHA and PT in the vaccinees is lower than from controls.[33,34] In the Göteborg trial of the mono-component pertussis toxoid, there was a significant rise of anti-FHA in about 95% of the vaccinees and the controls.[33] There was also a rise of PT antibody levels in 92% of controls but only in 50% of vaccinees. Positive cultures were obtained from 64% of controls and 51% of vaccinees ($P < 0.001$). If an increase in IgG FHA antibodies alone would have been used, the efficacy of the pertussis toxoid would have been 78% instead of 71%. The use of antigens in the vaccine for serologic diagnosis, therefore, results in removal of pertussis cases from recipients of multivalent vaccines who do not have a significant rise in their antibody levels to PT or to FHA and results in an overestimation of their efficacy.[15] Others have noted this problem; “… it can be noted that the use of the modified WHO case definition leads to the removal of a significant number of laboratory-confirmed cases in each vaccine group in the *B. pertussis*–specific group: 47%, 64%, and 12% of the cases were removed from the DT*a*P, DTP, and DT vaccine groups, respectively.”[34] Subtracting the cases from the controls (DT group), removed 35% of the cases in the DT*a*P group from calculation of vaccine efficacy. Although data, describing the percent of patients with ≥21 days of paroxysmal coughing and a negative culture but with no rise in PT and FHA antibody levels are not available from the placebo-controlled blinded studies, we propose that there is no statistically significant difference between the efficacy of multicomponent vaccines compared with that of pertussis

toxoid vaccine alone. The available data for up to 3 weeks of coughing justify this conclusion.

FHA ANTIBODIES DO NOT CONFER IMMUNITY TO PERTUSSIS

In mice, FHA does not confer immunity (protection) against intracerebral or pulmonary challenge with *B. pertussis* by active or by passive immunization with monoclonal or polyclonal antibodies.[35] Seroepidemiologic surveys show that pre-existing FHA antibodies, including those induced by infection with *B. parapertussis*, do not confer immunity to pertussis.[35–38] A cellular pertussis vaccine without FHA (Lederle Laboratories) had similar protective activity as vaccines containing FHA.[30,39 – 42] The addition of FHA does not confer additional protection to acellular pertussis toxoid vaccines or additional therapeutic effect to passively administered anti-PT.[39] There is no scientific basis for including FHA in a pertussis vaccine.

DOES PERTACTIN CONFER IMMUNITY TO PERTUSSIS IN MICE AND IN HUMANS?

Neither active nor passive immunity to pertactin confers protection to mice challenged intracerebrally.[38] After aerosol challenge in mice, pertactin conferred only incomplete protection, whereas pertussis toxoid conferred 100% protection at clinically relevant doses.[39] In humans, seroepidemiologic studies show that pertactin antibodies arise independently of pertussis infection[37] and these pre-existing pertactin antibodies do not prevent pertussis.[38,39] Infection with *B. parapertussis* induces antipertactin antibodies but does not prevent pertussis.[43] Japanese regulatory agencies have requirements only for FHA and pertussis toxoid. The experience in Japan with acellular vaccines, where pertussis has almost been eradicated, indicates that pertactin is not essential for vaccine-induced immunity to pertussis.[44]

FIMBRIA AS ANTIGENS FOR PERTUSSIS VACCINES

There are no published reports of potency assays in animals for fimbrial antigens. Further, pertussis vaccines that contain fimbria have shown no increased efficacy over those without this component.[45] Lastly, as with pertactin, the experience in Japan indicates that fimbria are not essential for vaccine-induced immunity to pertussis.[44]

MEASUREMENT OF SERUM PERTUSSIS TOXIN IgG ANTIBODY IS THE ONLY RELIABLE ASSAY FOR SEROLOGIC DIAGNOSIS OF PERTUSSIS

After the acute phase of pertussis has passed, measurement of the absolute level (not fold increase) of serum IgG anti-PT has been shown to be the only reliable assay for the serologic diagnosis of pertussis.[45– 47] “By using the cutoff value of 48 EU/mL, PT IgG was by far the most sensitive indicator of infection. PT has the advantage of being uniquely expressed by *B. pertussis* and discriminates between infection by *B. pertussis* and the antigenically related species *B. parapertussis*.”[47]

LOW LEVELS OF SERUM IgG ANTIPERTUSSIS TOXIN IN ADULTS CORRELATE WITH INCREASED SUSCEPTIBILITY TO PERTUSSIS

Low levels of PT antibodies were shown to be related to susceptibility to pertussis in children and young adults. More recently, the highest rate of pertussis in the United States and other developed countries, has been found in teenagers and adults.[48,49] Studies in these age groups provide evidence that high susceptibility to pertussis was associated with low or

nondetectable levels of serum IgG anti-PT, especially in those without pertussis vaccination or a history of pertussis.[50]

THE CONCENTRATION OF VACCINE-INDUCED IgG ANTIPERTUSSIS TOXIN CORRELATES WITH THE EFFICACY OF MONOCOMPONENT PERTUSSIS TOXOID VACCINE

IgG anti-PT was measured in 813 recipients 21 to 77 days after a third injection of a monocomponent pertussis toxoid.[51,52] Of these children, 126 were exposed to pertussis in their house. Those with severe pertussis had a median concentration of IgG anti-PT of 79 U/mL. Those with mild pertussis had 156 U/mL, and those without pertussis had 264 U/mL (79 vs. 246; $P < 0.0001$). Of the 687 children with pertussis but no household exposure, the median concentration of IgG anti-PT was 99 and 155 U/mL in those without pertussis (99 vs. 155; $P < 0.0001$). This study demonstrates a highly significant correlation between post vaccination PT IgG and protection against pertussis in children vaccinated with a monocomponent pertussis toxoid vaccine. Pertussis toxoid vaccines with greater immunogenicity, therefore, may be predicted to induce a higher degree of individual protection against the disease and the level of IgG anti-PT may be used as a surrogate for the efficacy of acellular pertussis vaccines.[53]

GENETICALLY-INACTIVATED PT HAS SUPERIOR IMMUNOGENICITY IN COMPARISON WITH CHEMICALLY-INACTIVATED PERTUSSIS TOXIN

Currently, the pertussis toxoid component of the licensed acellular vaccines is prepared by chemical inactivation of the toxin with aldehyde agents. But, the most immunogenic pertussis toxoid available is prepared from genetically-inactivated mutants and can be predicted to be more protective and for a longer duration than the current products.[42,54–56] The genetically-inactivated pertussis toxoid was shown to elicit higher levels of PT antibodies at lower levels of immunogen in adults, 2- to 4-year-olds, and in infants receiving their primary immunization compared with that elicited by licensed acellular pertussis.[52,57–59]

Pertussis cases reported to the CDC increased from 5158 to 21,503 in 2006 despite a high immunization rate of infants and children.[60] This increase was almost all due to cases over the age of 10 years, similar to that observed in Europe and in other developed countries.[61] Immunity and IgG anti-PT levels waned after vaccination as well as after disease. Booster doses, starting in adolescents and offered every 10 years, should maintain a high level of immunity in the population. So why did our children not receive the most immunogenic and likely the safest, pertussis toxoid? Unfortunately, pharmaceutical manufacturers have declined to produce genetically-inactivated mutant pertussis toxoid vaccines because of the expense required to meet the requirements of regulatory agencies and not for scientific reasons. But the change in the amino acid composition of the mutant toxoids is trivial, and there is clinical experience showing the safety and immunogenicity of the genetically-inactivated pertussis toxin at all ages.[62] A change from the currently available pertussis toxoid could be implemented easily. We affirm that it is imperative to provide the best pertussis vaccine to our children as soon as possible.

POSSIBLE REASONS FOR “VACCINE FAILURES” IN PREVENTING PERTUSSIS

Older children and adults were not immunized with cellular pertussis vaccines due to their unacceptable levels of toxicity in these age groups. Vaccine-induced and disease-induced

IgG anti-PT lasts only about 5 to 10 years, leaving these groups with an increased susceptibility to pertussis. In addition, the antivaccine movement, especially directed toward cellular pertussis vaccines, was responsible for many parents insisting that their children receive DT rather than DTP. We draw attention to the low levels of anti-PT in adolescents who were not immunized during infancy and childhood with a pertussis vaccine and were administered only 1 dose of Dt*a*P. As a hold-over from that time when cellular pertussis vaccines were used and publicity about their toxicity was widespread, personal exemptions were requested by concerned parents. These exemptions increased the risk of contracting pertussis and increased transmission of the disease in several communities.[63] Premature infants have a lesser IgG anti-PT response, especially those treated with cortico-steroids for respiratory distress.[62,64 – 66] Lastly, there is now an increased awareness of pertussis and more available diagnostic procedures for identifying pertussis as a cause of coughing disease in adults that has resulted in greater reporting of this disease.

CONCLUSIONS

A large body of evidence from many sources indicates that pertussis toxoid is both essential and sufficient for a pertussis vaccine. We have presented data that addition of other component(s) does not add to the immunity conferred by pertussis toxoid alone. The genetically-inactivated mutant toxin, the most immunogenic pertussis toxoid available, should be substituted quickly for chemically-inactivated toxoids. Mass immunization of adolescents, adults, and especially family members of newborns with acellular vaccines, will likely improve pertussis control in young infants. Lastly, a monovalent genetically-inactivated pertussis toxoid vaccine could be standardized by the same procedures as those used for diphtheria toxoid.

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