

Immunologic and Epidemiologic Experience of Vaccination With a Monocomponent Pertussis Toxoid Vaccine

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ABSTRACT. Pertussis re-emerged in Sweden with a cumulative incidence of about 60% during the first 10 years of life, when the locally produced cellular vaccine lost its efficacy around 1970 and general vaccination was discontinued in 1979. The epidemiology, clinical features, and immunology of pertussis and a monocomponent pertussis toxoid vaccine were studied in Göteborg, Sweden.

After phase 1 and 2 studies, a randomized, double-blind, placebo-controlled trial of pertussis toxoid (PTox), compounded with diphtheria and tetanus toxoids, was administered to 3450 children according to the Swedish schedule at 3, 5, and 12 months of age. After a mean follow-up of 18 months, the efficacy was 71% overall and 75% in household contacts, respectively. A statistically significant correlation was found between the level of PTox-induced antibodies and protection against pertussis. As observed with cellular and with multicomponent acellular vaccines, PTox reduced the severity of disease and the percent of children with positive cultures. Furthermore, vaccination reduced the transmission of *Bordetella pertussis* to household contacts in the vaccinees compared with the controls who received only diphtheria and tetanus toxoids. Patients with culture-verified *Bordetella parapertussis* infection reacted with antibodies to pertactin and to filamentous hemagglutinin but not to pertussis toxin, and some subsequently developed pertussis. The antibody responses of patients with pertussis to the surface polysaccharides of *B pertussis* and to *B parapertussis* were cross-reactive serologically. Serosurveys showed that only antibodies to pertussis toxin were related to the occurrence of pertussis in the general population: antibodies to filamentous hemagglutinin and pertactin were probably stimulated by antigens of other bacteria as well as *Bordetellae*.

Mass vaccination of Göteborg children born in the 1990s was started in 1995. In February 1999, about 55% had been vaccinated and both *B pertussis* and pertussis decreased significantly in individuals of all ages (herd immunity). Similar to diphtheria, PTox-induced immunity to pertussis occurs both on an individual and community basis.

The apparent greater efficacy of multicomponent acellular pertussis vaccines compared with monocomponent PTox was proposed to be an artifact created when the diagnosis of pertussis was made by the serologic criteria of the World Health Organization only. Our conclusion

is that PTox is both an essential and alone sufficient antigen in acellular pertussis vaccines. *Pediatrics* 2001; 108(6). URL: <http://www.pediatrics.org/cgi/content/full/108/6/e115>; *pertussis, pertussis toxoid, vaccine*.

ABBREVIATIONS. PTox, pertussis toxoid; WHO, World Health Organization; CI, 95% confidence interval; DT, diphtheria and tetanus toxoids; FHA, filamentous hemagglutinin; IgG, immunoglobulin G; LOS, lipooligosaccharide; LPS, lipopolysaccharide.

After changes in manufacturing during the late 1960s, vaccines composed of inactivated *Bordetella pertussis* (cellular vaccines) prepared by the National Bacteriologic Laboratory in Stockholm, Sweden, lost their potency and pertussis re-emerged in Sweden.¹ Routine vaccination of infants against pertussis was discontinued in 1979 and was reintroduced in 1996 with the availability of acellular vaccines. The studies on a monocomponent pertussis toxoid (PTox) vaccine to be described were initiated in 1986 in Göteborg, Sweden.

Based on Dr Margaret Pittman's hypothesis about the pathogenesis and immunity to pertussis,² we proposed that a suitably inactivated and immunogenic PTox was both essential and sufficient to prevent pertussis.³ Phase 1 and phase 2 studies showed that pertussis toxin treated with H₂O₂ (PTox) was safe and immunogenic in adults⁴ and children.^{5,6} An open study of clinical pertussis in children receiving the same vaccine and an age-matched nonvaccinated control group showed that the vaccine decreased the risk of pertussis in the vaccinees.⁷ On the basis of these studies, a randomized, double-blind, placebo-controlled trial of PTox (as a component of DTPTox) involving 3450 infants was conducted in Göteborg: children in the control group received DT.⁸ Diagnosis of pertussis followed the criteria of the World Health Organization (WHO).⁹ The data showed efficacy (71%; 95% confidence interval [CI]: 63%–78%) for at least 1.5 years and unchanged efficacy during a further open follow-up period of 6 months.^{8,10} Data from this trial confirmed our proposal that a suitable PTox was both essential and alone sufficient to prevent pertussis.^{2,3,8,11,12}

EFFECT OF VACCINATION WITH PT_{OX} IN VACCINEES EXPOSED TO HOUSEHOLD MEMBERS WITH PERTUSSIS

A subgroup of the study participants, who were exposed to pertussis in their households and could

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be expected to have a maximal exposure to *B pertussis*, was examined.¹³ Among these household contacts with pertussis, 20/99 (20%) were recipients of DTPTox compared with 64/79 (81%) who received the control vaccine (diphtheria and tetanus toxoids [DT]) (efficacy of 75%; 95% CI: 64%–84%). PTox, therefore protected equally well against pertussis both after community and household exposure. In 6 other reports, involving both cellular and acellular vaccines, in which the criteria for diagnosis of pertussis in household contacts were similar to that of the WHO: the reported efficacies (range: 42%–86%) were comparable to the monocomponent PTox.^{14–19}

EFFECT OF VACCINATION WITH PTox ON TRANSMISSION OF *B PERTUSSIS* TO HOUSEHOLD CONTACTS

The parents and siblings of the study participants were followed to determine if vaccination with PTox conferred indirect protection against pertussis (a prerequisite for herd immunity).²⁰ Pertussis was actively sought in the families of the vaccinees using the same WHO criteria as used for the clinical trial.^{8,9} There were 11 parents of PTox recipients and 26 parents of DT recipients (controls) who developed pertussis (60% protection; 95% CI: 16%–82%). In nonvaccinated younger siblings, there were 10 pertussis cases among siblings of PTox recipients and 18 cases of controls (43% protection, 95% CI: –31%–76%). Vaccination of children with the monocomponent PTox, therefore, reduced the transmission of *B pertussis* to household contacts.

STUDIES OF *B PARAPERTUSSIS*

Our interest in studying parapertussis was stimulated by the observation that children infected with this pathogen were not protected against pertussis.²¹ Although both *B pertussis* and *B parapertussis* cause a coughing disease, pertussis is much more frequent and causes more prolonged and severe coughing than parapertussis.^{22,23} A retrospective study of patients from whom *Bordetellae* were isolated revealed 58 patients with parapertussis: an incidence of 0.016/100 person-years in children 0 to 6 years of age and none in older children and adults. An active search for *Bordetella* infection, conducted during our placebo-controlled trial of PTox revealed 18 patients with parapertussis with an incidence of 0.2 cases/100 person-years with no difference between DTPTox and DT recipients: pertussis in DT recipients, in contrast, had an incidence of 16.2/100 person-years.²²

The genomes of the 3 major *Bordetella* species, *B pertussis*, *B parapertussis*, and *B bronchiseptica*, are highly similar with at least 2 exceptions.^{24–27} The first difference is that only *B pertussis* expresses pertussis toxin while the surface proteins of the 3 species of *Bordetellae* (filamentous hemagglutinin [FHA]), pertactin, fimbriae) are highly similar if not identical. Patients with parapertussis or pertussis responded with a similar and statistically significant increase in immunoglobulin G (IgG) antibodies to FHA and pertactin.²² Patients with parapertussis had no change in their IgG pertussis toxin antibodies whereas pertus-

sis elicited a significant increase to this protein. Four patients who had pertussis after an infection with *B parapertussis* have been described.²¹ The absence of pertussis toxin antibodies is the best explanation for the failure of *B parapertussis* to induce immunity to *B pertussis* and mirrors data from experimental infection of mice.^{28,29}

The second difference is that the surface saccharide of *B pertussis* is a lipooligosaccharide (LOS) composed of a core-like structure. *B parapertussis* and *B bronchiseptica*, in contrast, have a lipopolysaccharide (LPS) with an O-specific polysaccharide region composed of $\beta(1\rightarrow4)$ GalpANac extended from the core.³⁰ Geometric mean IgG anti-LOS from *B pertussis* and anti-LPS from *B parapertussis* increased significantly in 40 children with pertussis.³¹ IgG anti-LPS increased significantly in 14 children with parapertussis whereas all but 1 had nondetectable anti-LOS. Serum antibodies against LOS of *B pertussis* have been found in individuals without a history of a severe coughing disease. These natural LOS antibodies were probably stimulated by cross-reacting polysaccharides as described for other Gram-negative bacteria.³² Their presence in patients who later developed pertussis argues strongly against a protective role in *B pertussis* infection.³³

All these data confirm previous studies showing that only preexisting pertussis toxin antibodies were related to immunity to pertussis.^{34,35}

CORRELATION BETWEEN SERUM PERTUSSIS TOXIN IgG ANTIBODIES AND PROTECTION AGAINST PERTUSSIS

Pertussis toxin IgG antibodies were assayed 21 to 77 days after the third injection of PTox in 813 vaccinees.³⁶ Of these children, 126 were exposed to pertussis in their households and therefore can be considered to have sustained a maximal exposure to *B pertussis*. The median concentration of IgG anti-pertussis toxin was 79 U/mL in those with severe pertussis (≥ 21 days of paroxysmal cough), 156 U/mL in those with mild pertussis (< 21 days of paroxysmal coughing), and 246 U/mL in those who did not develop pertussis (79 vs 246; $P < .0001$). In the 687 vaccinees who had no household exposure, the median concentration of IgG anti-pertussis toxin was 99 U/mL in those with severe pertussis, 124 U/mL in those with mild pertussis, and 155 U/mL in those who did not develop pertussis (99 vs 155; $P < .0001$). These data show a highly significant correlation between the level of PTox-induced pertussis toxin IgG antibodies and protection against pertussis. The data provide evidence that assay of pertussis toxin antibodies may be used as surrogate for efficacy of acellular pertussis vaccines by regulatory agencies.³⁷

AGE-RELATED ACQUISITION OF SERUM IgG ANTIBODIES TO PT, FHA, AND PERTACTIN

Several serosurveys show that pertussis toxin antibodies follow infection only with *B pertussis*.^{22,33,34,38–41} Antibodies to FHA and pertactin, in contrast, are found in increasingly higher incidence as children grow older and their presence is often unrelated to a

history of pertussis.^{41,42} The stimulus for antibodies to these 2 proteins may be cross-reactive proteins on bacteria other than *Bordetellae*.⁴³

MASS VACCINATION WITH PT_{ox}

Mass vaccination of children born during the 1990s in the Göteborg area (population 778 597) was instituted in 1995 about 6 months after completion of the efficacy trial.⁴⁴ In February 1999, 55% of the children had received 3 injections of DTPT_{ox}. During the mass vaccination, *B pertussis* isolates decreased from 1200 to 64/year ($P < .0001$) and hospitalizations attributable to pertussis from 62 to 4/year ($P < .0001$). These decreases occurred in all age groups indicating that vaccination with PT_{ox} protected nonimmunized individuals (herd immunity) probably by inhibiting transmission of *B pertussis*.²⁰

MULTICOMPONENT ACELLULAR VACCINES

There is consensus that a PT_{ox} is an essential component of pertussis vaccines. Addition of variable numbers of other proteins to PT_{ox} has resulted in several multicomponent vaccines: bicomponent (PT_{ox} + FHA), tricomponent (PT_{ox} + FHA + pertactin), and pentacomponent (these 3 proteins + 2 fimbrial types). In controlled studies, the efficacy of multicomponent acellular vaccines were higher than observed with monocomponent PT_{ox}.⁴⁴⁻⁴⁸ This apparent greater efficacy may be attributable to a defect in the diagnostic criteria of the WHO.^{8,9,11,12} All multicomponent acellular vaccines contain FHA and PT_{ox}, both of which elicit antibodies. As has been observed in recipients of PT_{ox}, whether in cellular or acellular vaccines, there is a significant decrease in the number of positive cultures from pertussis cases in vaccinees compared with controls who develop pertussis.⁴⁹⁻⁵³ Accordingly, there is a greater reliance on the serologic diagnosis of patients with suspected pertussis in recipients of PT_{ox} compared with controls. In the clinical trial of monocomponent PT_{ox}, about 95% of patients (vaccinees and controls) who contracted pertussis had increases in their IgG anti-FHA levels. But an increase in serum IgG anti-pertussis toxin occurred in only about 50% in recipients of PT_{ox} compared with 93% in the controls ($P < .001$).³⁸ The use of an antigen for both vaccination and for serologic diagnosis by an antibody increase, therefore, is invalid. If cases with an increase in serum IgG anti-FHA without an increase in IgG anti-pertussis toxin would be disregarded, the efficacy of the PT_{ox} would have been about 80%.^{8,10} Similarly, if culture-negative cases in patients with ≥ 21 days of cough immunized with multicomponent acellular pertussis vaccines with no increases in anti-FHA were retained, it is likely that the efficacy estimate would be reduced by 5% to 10%.^{45,53,56} This observation was made initially comparing the efficacy of the JNIIH-6 (FHA + PT_{ox}) with JNIIH-7 (PT_{ox} alone).⁵³ According to Storsaeter et al, "A calculation with the 181 cases listed in Table 1 gives efficacy estimates of -7% for JNIIH-7 and 42% for JNIIH-6. However, such a crude comparison is based on the fact that the antigens used for diagnosis were also

used for immunization."⁴⁵ Others have confirmed that diagnosis of pertussis based on serologic data alone increases the apparent efficacy of multicomponent pertussis vaccines by removing a greater number of cases from these culture-negative subjects in the vaccinated groups compared with the unvaccinated controls. According to Stehr et al, ". . . 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 DTaP, DTP, and DT vaccine groups respectively." Thus, the lowest proportion of cases was removed from the DT group.⁵⁷

It is doubtful whether addition of other *B pertussis* components increases the efficacy of PT_{ox} alone.^{11,12} There is overwhelming evidence that FHA does not induce immunity. Cherry and Olin concluded, "The four-component vaccine's strength is that it contains pertactin and fimbriae-2 as well as PT and FHA. Its weakness is that it contains only modest amounts of PT, pertactin and fimbriae-2, it does not contain fimbriae-3 and has an abundance of FHA, which doesn't appear to contribute to protection."⁵⁶ By comparing the efficacy of multicomponent acellular pertussis of differing composition, Liese et al, reasoned, "Interestingly the protective efficacy of the SKB three-component was very similar to the efficacy of the two-component acP in our study, suggesting that the addition of pertactin did not result in a higher efficacy."⁵⁴ Pertussis has almost been eliminated in Japan by administration of acellular vaccines for which there are specifications only for PT_{ox} and FHA, which contain variable or trace amounts of pertactin and fimbriae.⁵⁸

There was also a decrease in the isolation rate of *B parapertussis* during this period.⁴⁴ This could be attributable to the finding that *B parapertussis* is frequently found concurrently with *B pertussis* during outbreaks.⁵⁹⁻⁶¹ Experiments in mice indicate that respiratory infection with *B pertussis* facilitates and prolongs colonization with *B parapertussis*.⁶²

LESS THAN OPTIMAL EFFICACY OF BOTH CELLULAR AND ACELLULAR PERTUSSIS VACCINES

On an individual basis, both cellular and acellular pertussis vaccines induce a less than optimal immunity against pertussis: estimates in double-blind studies range from 36% to 85%.^{8,47,48} The basis for immunity to pertussis remains controversial. Now there is a consensus that a critical level of IgG anti-pertussis toxin, whether induced by infection with *B pertussis* or by vaccination with cellular or acellular vaccines, is essential to confer immunity to pertussis. Yet, IgG anti-pertussis toxin does not kill or inactivate *B pertussis*. Our best explanation is that anti-pertussis toxin IgG inhibits the pharmacologic action of pertussis toxin that prevents phagocytic cells from killing *B pertussis*.^{63,64} This indirect effect provides an explanation for the less than optimal immunity induced by cellular and acellular vaccines.

SIMILARITIES BETWEEN THE EFFECTS OF DIPHtherIA TOXOID ON DIPHtherIA AND THOSE OF PTOx ON PERTUSSIS

The similarities of the individual and community effects of vaccination with a toxoid alone on immunity to diphtheria and pertussis are not commonly appreciated. First, antibodies to diphtheria toxin are not bactericidal to *Corynebacterium diphtheriae*: similar to that shown for pertussis, serum antitoxin inhibits the toxic action of diphtheria toxin on phagocytic cells.^{12,66} Second, the efficacy of vaccination with diphtheria toxoid on an individual basis is only about 70%.⁶⁶ Third, diphtheria can occur in patients with protective levels of antitoxin: as with pertussis, the level of antitoxin reduces the severity of disease compared with controls.⁶⁶ Fourth, elimination of diphtheria during outbreaks or epidemics requires vaccination of a large part of the population including children.⁶⁶ When at least 50% of the population has been vaccinated with the toxoid does elimination of diphtheria and eventually of tox⁺ *C diphtheriae* start to occur. In the United States and other developed countries, diphtheria has almost been eliminated despite the fact that a sizeable fraction of the population, approaching 50% in some parts, has less than protective levels of antitoxin. It is the virtual disappearance of tox⁺ *C diphtheriae* that accounts for the elimination of diphtheria from the population after prolonged mass vaccination. We propose that mass vaccination of a major part of the population with PTOx alone will produce the same effect on pertussis and *B pertussis*.^{12,66}

ANIMAL MODELS FOR VACCINE-INDUCED IMMUNITY TO PERTUSSIS

The potency of whole-cell vaccines has been reliably controlled by the mouse potency assay in which mice are vaccinated by 1 intraperitoneal injection and challenged intracerebrally 2 weeks later.^{2,11} The evidence is that this procedure is an assay of serum neutralizing antibodies to pertussis toxin.^{11,37} At clinically relevant levels, pertussis toxin is the only component of *B pertussis* that confers immunity in this model, either by active immunization or by passive immunization with polyclonal or monoclonal antibodies.¹¹ This is also true for intrapulmonary challenge of mice. But mice do not cough when infected with *B pertussis*, and predictably, do not transmit the pathogen to their littermates.

The essential role of pertussis toxin in the pathogenesis and immunity to pertussis is further illustrated in a pulmonary infection model of rats elicited by *B pertussis* capsulated with poly lactide-glucoside.⁶⁷ Parton et al improved the in vitro capsulation of *B pertussis* and showed that pertussis toxin is required to induce the lymphocytosis and paroxysmal coughing: strains of toxin-negative *B pertussis* and of *B parapertussis* do not induce these classical symptoms of pertussis in infants.^{68,69} Injection of wild-type *B pertussis*, but not of toxin⁻ strains or of *B parapertussis*, confers protection against challenge with the capsulated strains. Interestingly, injection of PTOx, but not FHA, pertactin, or fimbriae, conferred partial protection in this model.^{69,70}

CONCLUSION

Our experience with monocomponent PTOx in Göteborg during the past 16 years is reviewed along with results from other reports. Vaccination of infants with PTOx elicited 71% overall protection and 75% against household contacts, and, compared with controls, reduced the severity of disease, the percent of patients with pharyngeal cultures of *B pertussis*, and transmission of the pathogen to parents and younger siblings. There was a highly significant correlation between the postvaccination level of PTOx antibodies and protection against pertussis in vaccinees exposed in the community as well as those exposed in the home. Most importantly, mass vaccination of all children living in a defined area resulted in a marked reduction of *B pertussis* cultures and hospitalizations resulting from pertussis in all age groups. These individual and herd immunity effects observed with the monocomponent PTOx in Göteborg are similar to those exerted by whole-cell vaccines and multicomponent acellular pertussis vaccines. Finally, we showed that parapertussis, although eliciting similar levels of FHA and pertactin antibodies as pertussis, failed both to elicit pertussis toxin antibodies and to prevent pertussis.

Attention again was drawn to the similarities between immunity to diphtheria and pertussis. Mass vaccination of the entire population with diphtheria toxoid, another toxigenic respiratory pathogen confined to the epithelial surface, results in an incomplete level of immunity on an individual basis but eventually results in virtual elimination of tox⁺ *C diphtheriae* and diphtheria (herd immunity).

The results obtained in Göteborg show that mass vaccination with PTOx alone has the potential to induce herd immunity and to eliminate *B pertussis*. This is the ultimate goal for general vaccination against pertussis.⁷¹

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