Mass Vaccination of Children with Pertussis Toxoid—Decreased Incidence in Both Vaccinated and Nonvaccinated Persons

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During 1979–1995, there was no vaccination against pertussis in Sweden. With the aim of studying the epidemiology and transmission of pertussis, mass vaccination with pertussis toxoid of children born during the 1990s was instituted in the Göteborg area (population, 778,597) in 1995. Infants were offered 3 doses of pertussis toxoid combined with diphtheria and tetanus toxoids. Children aged ≥1 year were offered 3 doses of pertussis toxoid alone. From June 1995 through February 1999, 167,810 doses of pertussis toxoid were given to 61,219 children born during the 1990s (56% received 3 doses). The number of Bordetella pertussis isolates per year declined from 1214 (1993–1995) to 64 (January 1997 through June 1999; P < .0001), and hospitalizations due to pertussis declined from 62 to 5 (P < .0001). Significant decreases in B. pertussis isolates and hospitalizations occurred in all age groups, including adults and nonvaccinated infants. Thus, mass vaccination of children with pertussis toxoid decreases spread of B. pertussis in the population.

Several double-blind, placebo-controlled and open studies have shown that acellular pertussis vaccines, all of which contain pertussis toxoid alone or in combination with other antigens from Bordetella pertussis, induce protection against pertussis [1–7]. Although there is agreement that pertussis toxoid is essential for acellular pertussis vaccines, there is no agreement about the need for other components of B. pertussis in these vaccines. We believe that vaccination with pertussis toxoid alone is sufficient for protection [8], whereas others advocate that filamentous hemagglutinin, pertactin, and/or fimbriae in various combinations should be included [9–13]. Acellular vaccines with 1–5 components have been approved in North America and Europe. One argument against monocomponent pertussis toxoid vaccines is that although they are effective in preventing clinical pertussis, they may not prevent mild or subclinical infection with carriage and spread of the causative organism [9, 10, 13]. This is, however, contradicted by findings in a substudy of pertussis in family members of participants in a double-blind, placebo-controlled study of a monocomponent pertussis toxoid vaccine [2]: The incidence of pertussis was lower in parents and younger siblings of pertussis toxoid–vaccinated children than in parents and younger siblings of the nonvaccinated children in the control group [14]. The aim of the present study was to follow the incidence of pertussis during the introduction of a monocomponent pertussis toxoid vaccine in the Göteborg area of Sweden, a country that had not used effective
pertussis vaccines during the previous 25 years. Vaccination of infants with a whole cell pertussis vaccine, produced by the National Bacteriological Laboratory, was gradually introduced in Sweden during the 1950s. During the 1960s, the vaccination rate was >90% and pertussis had almost disappeared. Toward the end of the 1960s, several changes in the production of this whole cell vaccine resulted in an ineffective vaccine, and the incidence of pertussis returned to the prevaccination level despite a continued high vaccination rate [15–17]. The whole cell vaccine was withdrawn, and general vaccination against pertussis in Sweden ended in 1979. Between 1979 and 1995, <1% of all children were vaccinated with an imported whole cell vaccine. During the 1990s, trials of acellular pertussis vaccines were done but not to an extent that the epidemiology of the disease was affected.

STUDY DESIGN AND METHODS

Place and time of the study. The study took place in southwest Sweden in the city of Göteborg and 10 surrounding communities. During 1995–1998, the mean population was 778,597 and the mean annual birth cohort was 8915. The mass vaccination project started on 27 June 1995 and continued through 28 February 1999.

Study design, vaccines, and vaccinations. The study was an open, prospective study of the epidemiology of pertussis during the first years after introduction of a monocomponent pertussis toxoid vaccine, with use of historical controls. Infants were offered vaccination with a vaccine containing diphtheria, tetanus, and pertussis toxoids (DTP-toxoids) at 3, 5, and 12 months of age. Concurrently, they received a conjugated Haemophilus influenzae type b vaccine and inactivated poliovirus vaccine. The vaccines were given at Child Health Centers, which are attended by ~99% of all infants. Before the study started, infants had routinely received the same vaccines without pertussis toxoid at 3, 5, and 12 months of age. Children aged ≥1 year, who had already been vaccinated 3 times against diphtheria and tetanus, were offered vaccination with pertussis toxoid alone at study sites by nurses employed by the project. These children received 3 doses of pertussis toxoid with intervals of 2 and 6 months, respectively. Children who had been vaccinated at 3 and 5 months against diphtheria and tetanus were given 1 dose of DTP-toxoids at 12 months, followed by 2 doses of pertussis toxoid with intervals of 2 and 6 months. Finally, for children who had been incompletely vaccinated with whole-cell pertussis vaccine or with other acellular pertussis vaccines (children who moved into the study area), the vaccination series was completed with pertussis toxoid. All pertussis toxoid–containing vaccines were administered without charge to the parents or the Child Health Centers. From June 1995 through September 1998, the pertussis toxoid–containing vaccines were given subcutaneously in the left thigh to infants <1 year old and over the left deltoid muscle to older children. From October 1998, the vaccines were given intramuscularly. The aim of the study was primarily to vaccinate children born during the 1990s. The parents of these children were informed about the project at Child Health Centers, through advertisements in the press, and by individual letters. Children and adolescents born during the 1980s and the 1970s were not actively recruited but were vaccinated at the parents’ request.

After each vaccination, the 10-digit identification number of the vaccinated child and the vaccination date were reported to the central office of the project and entered into the database. A computer-based population register with the 10-digit identification numbers of all children born from 1 January 1990 and living in the study area was obtained every month from the statistical department of the city of Göteborg. This population register was merged with the database of the project for calculation of vaccination rate. When the mass vaccination project ceased on 28 February 1999, vaccination of infants with the same DTP-toxoids vaccine continued at the Child Health Centers without individual registration.

Each 0.5-mL dose of pertussis vaccine contained 40 μg of pertussis toxin inactivated by hydrogen peroxide. Each 0.5-mL dose of DTP-toxoids vaccine contained 25 flocculation units of diphtheria toxoid, 7 flocculation units of tetanus toxoid, and 40 μg of pertussis toxoid. The pertussis toxoid was produced by North American Vaccine (now acquired by Baxter Healthcare Corporation). The diphtheria and tetanus toxoids were produced by Statens Serum Institut. The vaccines were adsorbed onto aluminum hydroxide (0.5 mg Al/dose).

Study of pertussis epidemiology before and during the study. The effect of mass vaccination on the incidence of pertussis was evaluated by monitoring the numbers of isolates of B. pertussis and hospitalizations for pertussis in the study population. About 90% of all samples for culture for Bordetella from the study area are sent to the Bacteriological Laboratory at Sahlgrenska University Hospital in Göteborg. Culture samples from the periphery of the study area are sent to 1 of the 3 bacteriological laboratories in adjacent counties. Information on positive culture results from persons living within the area was obtained from the 4 laboratories from January 1993 through June 1999. Beginning in February 1993, PCR [18] was increasingly used to detect B. pertussis DNA in nasopharyngeal samples at the laboratory in Göteborg but not at the other 3 laboratories. From November 1996, all adult patients and the parents of all children with cultures positive for B. pertussis or positive results of PCR were interviewed by telephone concerning symptoms and vaccination status.

Data on hospitalizations for pertussis were obtained from the diagnosis registers at all 10 Departments of Pediatrics and of Infectious Diseases that admit patients from the study area and from the epidemiological center of the National Board of...
Health and Welfare in Stockholm, which receives reports on all hospitalizations from the whole country. All case records of patients with a discharge diagnosis of pertussis were reviewed. Patients who had neither documented symptoms of pertussis (cough with paroxysms, whooping attacks, or vomiting) nor laboratory confirmation were excluded. Hospitalization data from all sources were available from January 1990 through June 1999.

To estimate the use of other pertussis vaccines and the frequency of clinical pertussis, a questionnaire was sent to the parents of all children born during 1995–1998 and to a random sample of 10% of all children born during 1990–1994 who had not been vaccinated with pertussis toxoid. Questionnaires were sent to the parents of 4093 children in April 1999 and were completed by the parents of 3226 children (79%).

SeroLOGY. IgG antibodies to pertussis toxin were determined by ELISA of sera from 481 randomly selected children 4–6 weeks after they had received the third dose of DTP-toxoids. Two modifications of the originally described assay [2] were done; microtiter plates were not precoated with fetuin and results were calculated by a reference line comparison [19].

Statistics. To test if the observed decreases in positive culture results and in hospitalizations may be due entirely to chance, the incidences during the time periods January 1993 through December 1995 and January 1997 through June 1999 were compared by a test for the difference between 2 Poisson rates. The 1-tailed significance was calculated as $P(x \leq \text{number of observed “failures” } | n, p)$ where $x$ is a binomial random variable with expected value $n \times p$, $n$ is number of trials, and $p$ is probability of “failure” in 1 trial. Number of trials is the number of positive culture results or hospitalized cases, respectively, during both periods, and $p$ is risk years in the second period divided by risk years in both periods. “Failure” means that a positive culture result or a hospitalization occurred from January 1997 through June 1999. A 1-tailed test was used because the relevant alternative hypothesis was that the mass vaccination caused a decrease in positive culture results and hospitalizations. Population data for calculation of incidences (total population, population aged <6 months, and population aged ≥15 years) were obtained from yearly publications of the Göteborg Office of Statistics. The proportion of person-risk-years that fell in the second period was 46.2% for the total population, 41.5% for infants <6 months, and 44.6% for adults ≥15 years.

RESULTS

From 27 June 1995 through 28 February 1999, a total of 167,810 doses of pertussis toxoid were given to 61,219 children born on or after 1 January 1990. Table 1 shows numbers of doses of pertussis toxoid alone and DTP-toxoids given. Additionally, 4146 children born before 1 January 1990 received 11,686 doses of pertussis toxoid. Of the 65,365 children who received at least 1 dose of pertussis toxoid, 919 had previously been incompletely vaccinated with whole cell vaccine and 447 with another acellular vaccine.

Table 2 shows vaccination rates and estimated proportions of children with a history of pertussis at the start, in the middle, and at the end of the mass vaccination project. There were no significant differences in vaccination rates between the 11 par-

### Table 1. Numbers of doses of pertussis toxoid (PT) and of diphtheria-tetanus-pertussis toxoids (DTP-toxoids) given from 27 June 1995 through 28 February 1999 to children born on and after 1 January 1990 in mass vaccination project.

<table>
<thead>
<tr>
<th>Planned vaccination schedule</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTP-toxoids × 3 doses</td>
<td>30,019</td>
</tr>
<tr>
<td>DTP-toxoids + PT + PT</td>
<td>7208</td>
</tr>
<tr>
<td>PT × 3 doses</td>
<td>23,992</td>
</tr>
<tr>
<td>Total</td>
<td>61,219</td>
</tr>
</tbody>
</table>

### Table 2. Vaccination status and history of pertussis in children born during the 1990s and living in study area at the start, middle, and end of the mass vaccination project.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>June 1995</th>
<th>June 1997</th>
<th>February 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children born during 1990s</td>
<td>59,023</td>
<td>76,609</td>
<td>89,224</td>
</tr>
<tr>
<td>Pertussis toxoid × 3 doses, a %</td>
<td>4</td>
<td>43</td>
<td>56</td>
</tr>
<tr>
<td>Pertussis toxoid × 2 doses, a %</td>
<td>2</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Pertussis toxoid × 1 dose, a %</td>
<td>&lt;0.01</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Other acellular vaccine, b %</td>
<td>—</td>
<td>~0.5</td>
<td>~2</td>
</tr>
<tr>
<td>Whole cell vaccine, b %</td>
<td>~5</td>
<td>~4</td>
<td>~3</td>
</tr>
<tr>
<td>History of pertussis, b %</td>
<td>~20</td>
<td>~14</td>
<td>~10</td>
</tr>
<tr>
<td>No history of pertussis and not vaccinated, %</td>
<td>~70</td>
<td>~20</td>
<td>~20</td>
</tr>
</tbody>
</table>

a Calculations are based on merging of population register and database of project.
b Estimates are based on interviews with parents.
The vaccine coverage increased for each annual cohort during the 1990s. When the mass vaccination project ended, complete vaccination with 3 doses of pertussis toxoid had been achieved in 24% of the cohorts in 1990, 41% in 1991, 51% in 1992, 56% in 1993, 69% in 1994, 85% in 1995, 89% in 1996, and 89% in 1997.

Data on cultures positive for *B. pertussis* were also available for the time period 1977 through 1992 from the laboratory in Göteborg. The mean number of positive culture results from January 1993 through June 1995 was 101 per month (range, 62–154 per month). By the beginning of 1996, the number of isolates was lower than during any month before the project started. From January 1997 through June 1999, the number of isolates never exceeded 11 per month. The decrease in positive culture results was evident in both the target group for vaccination and in infants <6 months, who were too young to be completely vaccinated, and persons aged ≥15 years (figure 2). Comparisons of positive culture results for the time periods January 1993 through December 1995 and January 1997 through June 1999 were as follows: all ages, 3642 versus 159 (P < .0001), infants <6 months, 117 versus 10 (P < .0001), adults ≥15 years, 156 versus 7 (P < .0001).

Data on cultures positive for *B. pertussis* were also available for the time period 1977 through 1992 from the laboratory in Göteborg. The mean number of positive culture results was 80 per month (range, 11–261 per month). Peaks were seen every 2–3 years.

The addition of PCR as a diagnostic tool at the laboratory in Göteborg approximately doubled the number of laboratory-verified cases of pertussis. From January 1997 through June 1999, 75% of all samples were examined by both culture and PCR. *B. pertussis* was isolated from 94 patients, and an additional 91 patients had a positive result of PCR with negative culture result.

Figure 3 shows the total numbers of nasopharyngeal samples sent to the laboratories for culture for *B. pertussis* from persons living in the study area. About 75% of the cultures yielded negative results both before and during the mass vaccination.

From November 1996 (when structured interviews with all patients with positive culture results or their parents started) through June 1999, *B. pertussis* was isolated from 136 patients. Of the 109 children with positive culture results born during the 1990s, 74 were not vaccinated against pertussis, 22 were incompletely vaccinated with pertussis toxoid, 12 were vaccinated with 3 doses of pertussis toxoid, and 1 was vaccinated with whole cell pertussis vaccine. Twenty-seven persons with positive culture results were born before the 1990s. Of those, 23 were not vaccinated against pertussis, 1 was incompletely vaccinated with pertussis toxoid, and 3 were vaccinated with whole cell vaccine. *Bordetella parapertussis* was isolated from 22 patients in 1993, 21 in 1994, 22 in 1995, 10 in 1996, 9 in 1997, 1 in 1998, and 2 during the first 6 months of 1999.

A total of 460 patients with a discharge diagnosis of pertussis were hospitalized between 1 January 1990 and 30 June 1999. Of those, 29 were excluded because of poor documentation of symptoms and no laboratory confirmation of pertussis. The 29 excluded cases had the same yearly distribution as the 431 cases with documented clinical or laboratory verification of pertussis. Figure 4 shows the yearly distribution of these 431 cases. A decrease in hospitalizations for pertussis was evident from 1996 and occurred in all age groups, including infants <6 months and adults. Comparisons of numbers of hospitalizations for the time periods January 1993 through December 1995 and January 1997 through June 1999 were as follows: all ages, 185 versus 13 (P < .0001), infants <6 months, 55 versus 8 (P < .0001), adults ≥15 years, 11 versus 1 (P < .01).

Figure 2. Numbers of isolates of *Bordetella pertussis* per year from infants <6 months and adults ≥15 years in area of mass vaccination project.
Figure 3. Numbers of negative and positive results, in 6-month periods, of cultures for Bordetella pertussis obtained from inhabitants in 11 communities participating in mass vaccination project.

Figure 4. Hospitalizations for pertussis among inhabitants of 11 communities participating in mass vaccination project.

Serum IgG antibodies to pertussis toxin ranged between 10 and >400 U/mL (median, 224 U/mL; geometric mean, 198 U/mL) for the 481 infants from whom serum was obtained 4–6 weeks after the third dose of DTP-toxoids.

DISCUSSION

A combination of individual protection and decreased circulation of the causative organism induced by vaccination is considered to be of major importance for the control of many infectious diseases, such as diphtheria, measles, polio, and H. influenzae type b infection [20–22]. If vaccination protects against clinical symptoms only without preventing carriage and silent transmission, there is a risk that the morbidity will increase among nonvaccinated persons, such as infants, who are particularly susceptible to serious disease and death.

The present study provides evidence that transmission of B. pertussis in the population was interrupted by vaccination of children with the monocomponent pertussis toxoid vaccine. If the incidence of pertussis had been affected only by individual vaccine efficacy (point estimate, 71% after 3 doses [2]), vaccination rate (56% had received 3 doses at the end of the project), and disease-induced immunity (≈10%; table 2), it should have decreased by <50% and the decrease should have been evident only toward the end of the mass vaccination project. Instead, pertussis, as diagnosed by positive culture results, had decreased by >90% after 2 years. The disease incidence also decreased significantly in infants <6 months and in adults. The protection achieved in these age groups can be attributed only to a decrease in the circulation of the organism achieved by vaccination of children aged ≥1 year.

Isolates of B. pertussis from nasopharyngeal cultures reflect the incidence of pertussis but give no accurate estimate of its true incidence. A possible source of bias in the part of the present study presenting cultures positive for B. pertussis must therefore be acknowledged. The total number of nasopharyngeal cultures sent to the laboratories for culture for Bordetella decreased markedly, as did the numbers of isolates of B. parapertussis. Because this organism does not express pertussis toxin, a pertussis toxoid vaccine should not affect the incidence of this infection, unless data indicating that infection with B. pertussis facilitates and prolongs infection with B. parapertussis in mice are relevant also for humans [23].

The demonstration of a decrease in hospitalizations due to pertussis during the mass vaccination project provides stronger evidence of decreased transmission than does the decrease in the number of B. pertussis isolates. There were pronounced decreases in the numbers of hospitalizations due to pertussis in all age groups, both in those targeted for mass vaccination and in infants and adults. If the vaccine had induced only individual protection without affecting the circulation of the organism, the rate of hospitalizations of infants and adults should have been unchanged.

A possible source of overestimation of vaccine effectiveness in the present study could be that there was an overlap between the historical control period in the present study and the previously mentioned efficacy trial from January 1993 through July 1994 [2]. During this period, there were 1946 isolates of B. pertussis, of which 388 (20%) came from participants in the efficacy trial or their family members. None of the participants in the efficacy trial were hospitalized.

The results of the present study must be considered in relation to the epidemiology of pertussis in the rest of Sweden. If a pronounced decrease in the incidence of the disease had occurred earlier or concurrently in the rest of Sweden, the decrease in the Göteborg area could have been partly explained by a lower influx of new cases from the surrounding areas. This was, however, not the case. Figure 5 shows the monthly distribution of B. pertussis isolates as reported from all Departments of Bacteriology in Sweden to the Swedish Institute.
for Infectious Disease Control (Stockholm), with exclusion of isolates from persons living in the area of the Göteborg mass vaccination project. The decrease in the Göteborg area preceded the decrease in the rest of the country, in which routine vaccination of infants was introduced during the spring of 1996. Organized “catch-up” vaccination of older children was done in only some counties in the rest of Sweden.

The favorable results of the present study should not be interpreted to indicate that pertussis can be controlled by vaccination of infants and young children only. When the mass vaccination project started, pertussis had been endemic in the area for ~20 years and the majority of children and adolescents born during the 1970s and 1980s and of adults had experienced the disease and had natural immunity. Because it can be expected that vaccine-induced immunity wanes with time, administration of booster doses to adolescents and adults who were vaccinated as infants should be considered. The epidemiology of pertussis must be continuously surveyed as long as the disease exists in any part of the world.

Acknowledgments

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