MAJOR ARTICLE

Effects of Pertussis Vaccination on Disease: Vaccine Efficacy in Reducing Clinical Severity

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We estimated the effectiveness of pertussis vaccination in reducing the clinical severity of breakthrough disease among vaccinated individuals from a comprehensive follow-up study of a community of 30,000 residents of Niakhar, Senegal, in 1993. A physician examined all children with potential pertussis (cough of >7 days' duration). Samples were collected from 97% of these children for culture or serologic testing as part of the active surveillance for a pertussis vaccine trial. Cases of pertussis were defined by confirmation through culture or serologic testing or by a history of contact with a person with culture-confirmed pertussis. Among children with confirmed cases, severity of illness was assessed according to a scale that combined clinical signs and symptoms. The efficacy of the vaccine in reducing disease severity was 48% (95% confidence interval, 39%–55%) among children vaccinated with 3 doses of whole-cell (67%) or acellular (32%) vaccine. Primary cases were more severe than secondary cases in residential compounds. Pertussis vaccination is effective in reducing the severity of illness.

Pertussis affects all age groups and can occur in immunized or previously infected individuals [1–3]. The disease features a broad spectrum of illness that ranges from asymptomatic to life-threatening.

The relatively mild character of pertussis illnesses in vaccinated children, compared with that in unvaccinated children, was reported as early as the 1930s, by Kendrick and Eldering [4]. Indeed, many studies report that vaccination has a beneficial effect on the severity of the disease [2, 5–10], although other studies have found no difference [11]. Usually individual symptoms are studied separately. However, the multitude of pertussis symptoms suggests that creation of a scale to assess the global severity of a pertussis illness, together with a definition for pertussis infection, is required.

More accurate evaluation of the effect of pertussis vaccine on the clinical severity of disease would improve our understanding of the complete spectrum of the effects of pertussis vaccination. In this article, we propose a scale to assess the global clinical severity of a pertussis case. We then propose a method of estimating the efficacy of vaccine in reducing the clinical severity of illness, with the condition that the case of pertussis has been confirmed by culture or serologic testing [12].

Received 17 February 2003; accepted 6 May 2003; electronically published 23 August 2003.

Financial support: National Institutes of Health (grant R01-AI32042); French Ministry of Foreign Affairs (research grant Lavoisier), Singer-Polignac Foundation (subvention), and Aventis Pasteur (consultancy fees) (all to M.-P.P.). Data collection was financed by the Institut de Recherche pour le Développement and Aventis Pasteur; between 1983 and 1989, data collection was partially funded by the European Economic Community (grant TDR 36) and the Task Force for Child Survival (grant 428).

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Clinical Infectious Diseases 2003; 37:772–9

1058-4838/2003/3706-0005$15.00

METHODS

Setting and population. The Niakhar study area is located 150 km southeast of Dakar, Senegal, and includes 30 villages. Extended families reside in compounds. In January 1993, there were 26,306 residents living in 1800 compounds [13]. Since March 1983, all

residents have been under longitudinal observation, based on annual or, since 1987, weekly visits to compounds [14]. Pertussis vaccine studies were conducted in this area in the 1990s, in accordance with the Helsinki Declaration [15, 16]. As described elsewhere [15, 17], pertussis was endemic, with epidemics every 3–4 years, and 1993 was a pertussis epidemic year. The present analysis was restricted to children <15 years of age who had potential cases of pertussis in 1993.

Pertussis immunization. The Expanded Programme on Immunization was implemented in 1987. Infants received diphtheria and tetanus toxoids, whole-cell (WC) or acellular (AC) pertussis vaccine (2 components, pertussis toxin [PT] and filamentous hemagglutinin [FHA]), and inactivated poliomyelitis vaccine (Tetracoq [WC] and Tetravac [AC]; Aventis Pasteur) [15, 18]. As a result, by 1993, the population vaccine coverage had increased steadily, to 77% and 19% among children <5 and 5–14 years of age, respectively [17]. All vaccine doses were documented, and extensive checks were performed [15, 17].

Pertussis surveillance. Active surveillance of pertussis was conducted in children <15 years of age. Trained, supervised field workers visited every compound weekly. They reported cases in children <15 years old who had potential pertussis (cough of >7 days's duration) weekly to experienced physicians who assessed each illness. Unless another disease, such tuberculosis or malaria, was definitively diagnosed, the physician visited every compound in which such a child was present weekly to ascertain whether any further cases had developed, until every affected child in the compound had stopped coughing. Older residents were included in the surveillance only if they developed potential cases. The physician was blinded to the vaccination status (vaccinated vs. unvaccinated and AC vs. WC) of the children. In addition, the physician collected laboratory samples from all consenting potential individuals. Nasopharyngeal aspirates were drawn for isolation of *Bordetella pertussis* or *Bordetella parapertussis* and for detection of *B. pertussis* DNA via PCR. Blood samples (acute- and convalescent-phase serum samples) were obtained for measurement of IgG titers to PT or FHA by ELISA [15, 19]. Erythromycin prophylaxis was administered to all infants <6 months of age who were living in compounds in which individuals with potential pertussis were present.

Definitions. Confirmation of pertussis infection was based on the presence of at least 1 of 3 laboratory criteria: (1) isolation of *B. pertussis* from a nasopharyngeal aspirate ("culture positive"), (2) significant increase or decrease in PT or FHA antibodies (100% change between convalescent- and acute-phase serum samples; "serology positive") [19], and (3) signs and symptoms of disease in an individual who lived in the same compound as a child who had onset of culture-positive disease within 28 days.

Severity of illness was assessed according to the scale shown in table 1. "Severe disease" was defined by a score greater than a particular threshold value. The main outcome measure was defined using the overall severity median score for the population. In this study, it was 6. The scale includes clinical signs and symptoms recorded by physicians during weekly visits. Death was not included in the scale, because only 1 death attributed to pertussis occurred during the study period, in an unvaccinated 2-month-old infant [17].

"Primary cases" were those in which the date of onset was within 6 days of the onset of the first case in the compound (i.e., the home or residential unit). All cases that occurred ⩾7 days after the first case were considered to be "secondary cases."

Data analysis. Vaccine efficacy in slowing disease progression (VEp) [12], here, in reducing severity, was a measure of the decreased severity of breakthrough disease compared with disease in unvaccinated individuals. It was measured by subtracting the relative risk of severe disease in vaccinated children, compared with unvaccinated children, who had confirmed cases of pertussis from 1: VEp = 1 − [(severe vaccinated cases/all vaccinated cases)/(severe unvaccinated cases/all unvaccinated cases)]. Sex, age, and type of case (primary or secondary) were included in a multivariate analysis in which logistic regression was used. Significant factors were subsequently retained in the analysis to give adjusted estimates of vaccine efficacy, and the regression coefficients were transformed back to the relative risk scale [20]. The bootstrap method was used to compute 95% CIs for VEp [21].

Vaccine efficacy in reducing susceptibility (VEs) was the usual

Table 1. Scale used to assess the severity of illness among children with symptoms of pertussis.

Variable	No. of points
Severity of cough	
Typical paroxysms with whoops	4
Typical paroxysms without whoops	3
Atypical paroxysms only	1
Apnea	6
Pulmonary sign[a]	3
Mechanical complication[b]	3
Facial swelling	3
Conjunctival injection	3
Post-tussive vomiting	2
Total score (severity)[c]	
Mild disease	⩽6
Severe disease	>6

[a] Bronchitis or bronchopneumonia, as diagnosed by a physician on auscultation.
[b] Subconjunctival hemorrhage or umbilical or unguinal hernia.
[c] The overall median total score was 6 in this study.

measure of the protective effect of vaccination based on the number of events per child-years at risk. It was measured by subtracting the incidence rate ratio for all confirmed cases or for cases with severe disease from 1: VEs = 1 − [(all or only severe vaccinated cases/child-years at risk among all vaccinated children)/(all or only severe unvaccinated cases/child-years at risk among all unvaccinated children)]. Child-years at risk was computed for the calendar year 1993 among susceptible children between 6 months and 8 years of age (i.e., children with no recorded history of pertussis). To be consistent, only children with no history of pertussis were considered. In computing 95% CIs for VEs, the log normality of the relative risks was assumed [22].

To assess potential bias in the selection of confirmed cases, we examined clinical illnesses among children with potential cases of pertussis whose culture and serologic test results were negative and among children for whom no laboratory samples were collected. We also looked at the distribution of positive laboratory test results among vaccinated and unvaccinated children. The statistical test of differences among dichotomous variables was either Pearson's χ^2 test or Fisher's exact test, as appropriate; for continuous variables, the Wilcoxon rank-sum test was applied. All *P* values are 2-sided. The analysis was done using SAS, version 8.2 for Unix (SAS Institute).

RESULTS

Population selection. In 1993, 2123 individuals with potential cases of pertussis (cough of >7 days' duration) were identified in 518 of 1800 residential compounds. Of these, 2080 (98%) were children <15 years of age. The majority of the children, 1657 (78%) of 2123, were either unvaccinated ($n = 813$) or completely vaccinated with 3 doses of a pertussis vaccine ($n = 844$). In this group of 1657, all of the 85 children who were <6 months of age and almost all ($n = 378$) of the 382 children who were ⩾9 years of age were unvaccinated. Both of these groups of children were excluded, because no comparison of the severity of illness between unvaccinated and vaccinated cases could be performed. Thus, 1190 (72%) of 1657 children who were 6 months to 8 years of age were included in the analysis. These children represented 75% (1190 of 1584) of the potential cases in that age group. Three hundred fifty (29%) of these 1190 children were unvaccinated, and 840 (71%) had received 3 doses of a pertussis vaccine; 568 (68%) of those 840 received a WC vaccine, and 261 (31%) received an AC vaccine. Only 11 children (1%) had received doses of both vaccines alternately.

Laboratory confirmation. Among the 1190 children with potential cases of pertussis, information fulfilling 1 of the criteria for laboratory confirmation criterion was available for 98%: at least 1 test (culture or serologic test) was done for 1156 children, and culture was done for home contacts of 9 children who were not tested themselves. Thus, only 25 children had cases that were not confirmed by laboratory findings (19 [5%] of the 350 unvaccinated children and 6 [0.7%] of the 840 vaccinated children). Culture and serologic tests were done for 813 children (68%; 198 [57%] of unvaccinated and 615 [73%] of vaccinated children). Only culture was done for 342 children (29%; 129 [37%] of unvaccinated and 213 [25%] of vaccinated children). Of the remaining 10 children, 1 vaccinated child had only serologic tests done, but culture was done using samples from that child's contacts, and 9 children (4 unvaccinated and 5 vaccinated) had no tests done, but culture was done using samples from their contacts.

B. pertussis was isolated from samples from 272 (24%) of the 1155 children for whom cultures were done (103 [32%] of 327 unvaccinated and 169 [20%] of 828 vaccinated children). The results of serologic tests were positive for 545 (67%) of

Table 2. Confirmation criteria for potential cases of pertussis in 834 children ages 6 months to 8 years for whom pertussis was confirmed by laboratory testing and who had or not received pertussis vaccine.

	No. (%) of cases		
Laboratory results	All ($n = 837$)	In unvaccinated children ($n = 243$)	In vaccinated children ($n = 594$)
Test done			
Culture	832 (99)	240 (99)	592 (99)
Serologic testing	661 (79)	168 (69)	493 (83)
Test results positive			
Culture and serologic testing	157 (19)	57 (23)	100 (17)
Culture only	115 (14)	46 (19)	69 (12)
Serologic testing and culture for a contact	196 (23)	37 (15)	159 (27)
Serologic testing only	192 (23)	49 (20)	143 (24)
Culture for a contact only	177 (21)	54 (22)	123 (21)

the 814 children from whom 2 blood samples were obtained (143 [72%] of 198 unvaccinated and 402 [65%] of 616 vaccinated children). The first nasopharyngeal aspirate and the first blood sample were obtained at a median of 11 days (interquartile range [IQR], 9–16 days) after onset of cough among both unvaccinated and vaccinated children. The median interval between the times at which the 2 blood samples were collected was similar among unvaccinated and vaccinated children (46 days for both; IQR, 35–62 days).

Laboratory-confirmed cases. In all, 834 children (70%) with potential cases of pertussis had pertussis confirmed by culture or serologic testing or had contact with an individual with a culture-confirmed case. Three children (1 unvaccinated child and 2 vaccinated children) had 2 episodes of laboratory-confirmed clinical illness each, for a total of 837 cases of laboratory-confirmed pertussis. The proportion of confirmed cases was similar in the unvaccinated (243 [69%] of 350 children) and vaccinated (594 [71%] of 840 children) groups. Among the 594 vaccinated children with confirmed cases, 397 (67%) had received a WC pertussis vaccine, and 188 (32%) had received an AC pertussis vaccine. Nine children had received doses of both vaccines alternately. The criteria for laboratory confirmation among these children are shown in table 2.

Among children with confirmed cases, 123 (51%) of the 243 who were unvaccinated were girls, compared with 315 (53%) of the 594 who had been vaccinated. The median age was 6.5 years (IQR, 4.4–7.8 years) in the unvaccinated, laboratory-confirmed group and 3.6 years (IQR, 2.1–5.0 years) in the vaccinated, laboratory-confirmed group. Eighty-four unvaccinated children (35%) and 141 vaccinated children (24%) with confirmed pertussis had primary cases. Among all 837 children with confirmed cases, only 6% had a previous history of pertussis (8% of unvaccinated and 5% of vaccinated children). Among healthy children in the same age group, 22% had a previous history of pertussis (40% of unvaccinated children and 15% of vaccinated children).

Reduction in severity. The characteristics of clinical illness in 834 children with 837 cases of confirmed pertussis are pre-

Table 3. Characteristics of clinical illness in 837 cases of laboratory-confirmed pertussis in 834 children ages 6 months to 8 years who had or had not received pertussis vaccine.

Variable	Cases in unvaccinated children (n = 243)	Cases in vaccinated children (n = 594)[a]	P
Paroxysms	176 (72)	281 (47)	<.0001
Typical with whoops	83 (34)	96 (16)	<.0001
Typical without whoops	21 (9)	27 (5)	.02
Atypical only	72 (30)	158 (27)	.37
Both atypical and typical	88 (36)	98 (17)	<.0001
Apnea	3 (1)	0	.006
Cyanosis	0	0	
Alteration of consciousness or seizures	0	0	
Pulmonary sign	29 (12)	57 (10)	.31
Mechanical complication	4 (2)	7 (1)	.59
Facial swelling	115 (47)	148 (25)	<.0001
Conjunctival injection	222 (91)	389 (65)	<.0001
Post-tussive vomiting	180 (74)	367 (62)	.001
Post-tussive sticky sputum	228 (94)	513 (86)	.002
Sneezing	224 (92)	525 (88)	.1
Runny nose	200 (82)	501 (84)	.47
Duration of illness, median days (IQR)	99 (71–134)	90 (55–126)	.002
Severity of illness[b]			
Median score (IQR)	8 (5–12)	5 (3–9)	
Mild disease	94[c] (39)	404[c] (68)	<.0001
Severe disease	149[c] (61)	190 (32)	

NOTE. Data are no. (%) of cases, unless otherwise indicated. IQR, interquartile range.

[a] All children had received at least 3 doses of pertussis vaccine; only 9 children (1.5%) had received 4 doses, of whom 5 had mild and 4 had severe disease.

[b] The scale used to assign the severity score is shown in table 1. The overall median score was 6. A score ⩽6 indicates mild disease; a score >6 indicates severe disease.

[c] Three children had 2 episodes of laboratory-confirmed clinical illness: 1 unvaccinated child had 1 mild and then 1 severe episode, and 2 vaccinated children had 2 mild episodes each.

Table 4. Number of cases of severe pertussis, among 834 children who had or had not received pertussis vaccine, and efficacy of the vaccine in reducing severity, according to severity score.

Score	No. (%) of cases			Vaccine efficacy,[a] % (95% CI)
	All (n = 837)	In unvaccinated children (n = 243)	In vaccinated children (n = 594)	
>0	738 (88)	233 (96)	505 (85)	11 (8–15)
>1	728 (87)	231 (95)	497 (84)	12 (8–16)
>2	677 (81)	227 (93)	450 (76)	19 (14–23)
>3	559 (67)	205 (84)	354 (60)	29 (23–35)
>4	529 (63)	194 (80)	335 (56)	29 (22–36)
>5	443 (53)	178 (73)	265 (45)	39 (32–46)
>6	339 (41)	149 (61)	190 (32)	48 (39–55)
>7	315 (38)	139 (57)	176 (30)	48 (39–56)
>8	268 (32)	119 (49)	149 (25)	49 (38–58)
>9	151 (18)	76 (31)	75 (13)	60 (47–70)
>10	147 (18)	75 (31)	72 (12)	61 (48–71)
>11	130 (16)	67 (28)	63 (11)	62 (48–72)
>12	31 (4)	20 (8)	11 (2)	78 (54–89)
>13	30 (4)	19 (8)	11 (2)	76 (51–89)
>14	24 (3)	17 (7)	7 (1)	83 (60–93)

NOTE. The scale used to assign the severity score is shown in table 1. The overall median score was 6. A score ⩽6 indicates mild disease; a score >6 indicates severe disease.

[a] Vaccine efficacy in slowing disease progression (VEp) was calculated using the following formula: VEp = 1 − [(severe vaccinated cases/all vaccinated cases)/(severe unvaccinated cases/all unvaccinated cases)].

sented in table 3. The overall median total score for illness severity was 6. On the basis of this threshold value of 6, 61% of unvaccinated children were considered to have severe disease, compared with 32% of vaccinated children. Thus, the estimated VEp was 48% (95% CI, 39%–55%). Unvaccinated children were twice as likely as vaccinated children to have severe disease. To examine the sensitivity of the results to the choice of the threshold value, we estimated VEp using values from 1 to >14 (table 4). The estimated VEp varied from 11% to 83%, and in each case the lower limit of the 95% CI was >0. Thus, the significant effect of vaccination on preventing severe clinical cases was robust to the choice of threshold value for severity.

Duration of illness was higher among children with severe disease than among those with mild disease (median duration, 112 days [IQR, 82–139 days] vs. 80.5 days [IQR, 47–116 days], respectively), regardless of vaccination status ($P < .0001$). Percentages of severe clinical illnesses, according to the vaccine previously received, were 35% (137 of 397 children) for WC vaccine and 27% (50 of 188 children) for AC vaccine ($P = .06$). Children vaccinated with the WC formulation were older than those who had received the AC vaccine (median age, 4.5 years [IQR, 3.1–5.6 years] vs. 2.2 years [IQR, 1.5–3.2 years], respectively). Consequently, breakthrough cases in children who had received the WC vaccine occurred longer after vaccination (median time between vaccination and illness, 3.6 years [IQR, 2.5–4.5 years]) than did breakthrough cases in children who had received the AC vaccine (1.7 years [IQR, 0.9–2.5 years]) ($P < .0001$). Thus, 90% of the children who had received the AC vaccine had been vaccinated within 3 years, compared with only 32% of those who had received the WC vaccine. The proportion of children with severe cases in each group was similar (17% for WC vaccine vs. 25% for AC vaccine among children with cases that occurred <3 years after vaccination and 43% for WC vaccine vs. 44% for AC vaccine among children with cases that occurred ⩾3 years after vaccination).

Secondary results. The VEs, which was calculated on the basis of child-years at risk, was 64% (95% CI, 55%–71%) for children with severe disease (using a threshold value of 6) and 29% (95% CI, 19%–39%) among all children with confirmed cases. Table 5 presents the characteristics of clinical illnesses in the 25 children (of 1190 children included in the study) who were not tested and in the 152 children (of 813 children for whom tests were done) who had negative results of all laboratory tests done. No statistically significant difference in severity of illness was found between unvaccinated and vaccinated children with negative results of testing. The estimated VEp was 39% (95% CI, −26% to 70%) among children with potential but unconfirmed cases of pertussis. In the group of

Table 5. Characteristics of clinical illness in 177 children ages 6 months to 8 years for whom the results of all tests for pertussis were negative or who were not tested and who did or did not receive pertussis vaccine.

Variable	Children with negative results of all tests			Children not tested		
	Unvaccinated (n = 30)	Vaccinated (n = 122)	P	Unvaccinated (n = 19)	Vaccinated (n = 6)	P
Paroxysms	10 (33)	28 (23)	NS	12 (63)	1 (17)	NS
Typical with whoops	2 (7)	1 (1)	NS	7 (37)	0	NS
Typical without whoops	1 (3)	3 (3)	NS	2 (11)	0	NS
Atypical only	7 (23)	24 (20)	NS	3 (16)	1 (17)	NS
Both atypical and typical	3 (10)	2 (2)	.05	3 (16)	0	NS
Apnea	0	0	NS	0	0	NS
Cyanosis	0	0	NS	0	0	NS
Alteration of consciousness or seizures	0	0	NS	0	0	NS
Pulmonary sign	2 (7)	13 (11)	NS	1 (5)	1 (17)	NS
Mechanical complication	0	0	NS	0	0	NS
Facial swelling	11 (37)	16 (13)	.003	7 (37)	0	NS
Conjunctival injection	25 (83)	60 (49)	.0007	16 (84)	1 (17)	.01
Post-tussive vomiting	16 (53)	62 (51)	NS	14 (74)	4 (67)	NS
Post-tussive sticky sputum	25 (83)	95 (78)	NS	18 (95)	6 (100)	NS
Sneezing	26 (87)	104 (85)	NS	14 (74)	6 (100)	NS
Runny nose	20 (67)	95 (78)	NS	15 (79)	3 (50)	NS
Duration of illness, median days (IQR)	65.5 (49–123)	58 (35–85)	NS	115 (87–141)	107.5 (16–149)	NS
Severity of illness[a]						
Median score (IQR)	5 (3–8)	3 (1–5)		8 (5–9)	2.5 (0–5)	
Mild disease	22 (73)	102 (84)	NS	8 (42)	6 (100)	.02
Severe disease	8 (27)	20 (16)		11 (58)	0	

NOTE. Data are no. (%) of children, unless otherwise indicated. IQR, interquartile range; NS, not significant.

[a] The scale used to assign the severity score is shown in table 1. The overall median score was 6. A score ⩽6 indicates mild disease; a score >6 indicates severe disease.

children from whom no laboratory samples were obtained, illnesses appeared to be more severe among unvaccinated children than among vaccinated children, but the number of children in this group was small.

Primary cases were more severe than secondary cases, regardless of the vaccination status of the child. Among unvaccinated children, 63 (75%) of 84 primary cases were found to be severe, compared with 86 (54%) of 159 secondary cases ($P = .002$). Likewise, among vaccinated children with breakthrough cases, 62 (44%) of 141 primary cases were severe, compared with 128 (28%) of 453 secondary cases ($P < .0005$). Overall, culture results were positive more often for children with severe disease (41%) than for children with mild disease (27%) ($P < .0001$; 50% vs. 31%, respectively, among unvaccinated and 34% vs. 26% among vaccinated children).

In a multivariate analysis, sex was not found to have any effect on the relative risk of severe disease or the corresponding VEp, whereas the type of case (primary or secondary) and the age of the child did. Age had an effect only in the vaccinated group. The interpretation of both VEp and VEs adjusted for age was hindered as a result of this age–vaccination status interaction. When children were separated into 2 age groups, <4 and ⩾4 years, a significant interaction was found in the older group only ($P = .01$). Time since vaccination was then introduced in the model, instead of age. The adjusted VEp estimates were 65% (95% CI, 56%–73%) for children vaccinated within <3 years of the onset of illness and 30% (95% CI, 18%–41%) for those vaccinated ⩾3 years before the onset of illness. When the analysis was adjusted both for time since vaccination and for type of case, the VEp estimates for secondary cases were similar to those given above, but the VEp estimates for primary cases were lower (55% [95% CI, 45%–65%] and 24% [95% CI, 13%–34%], respectively).

DISCUSSION

These results indicate that pertussis vaccination substantially decreases the severity of breakthrough disease in children who receive 3 doses of vaccine, compared with that in unvaccinated children. The majority of the vaccinated children who devel-

oped pertussis experienced mild disease, regardless of whether they had previously received a WC or an AC vaccine. Protection against severe disease was greater in recently vaccinated children than in children who had been vaccinated ⩾3 years before the onset of illness. Our finding that immunization moderates the severity of the clinical manifestations is consistent with other reports [2, 4–10]. Laboratory samples were not obtained from asymptomatic children, and therefore we could not estimate the efficacy of the vaccine in preventing infection. We found that duration of illness was associated with severity, regardless of vaccination status. Our finding of more-severe illness in children with primary cases than in children with secondary cases suggests that a relationship exists between intensity of exposure and severity of disease (as has been suggested elsewhere [6, 23]), if the type of case is considered to be a rough surrogate for levels of intensity of exposure.

Two aspects of our efficacy estimates differ from most others used to measure the efficacy of pertussis vaccination. First, we developed a global measure of severity, as has been done for other infectious diseases [24, 25]. Usually, when the clinical severity of pertussis disease in vaccinated and unvaccinated groups is compared, each symptom is considered individually [4, 5, 7]. Second, we studied the effect of vaccination on clinical severity (VEp) in symptomatic, infected children only. Although protective efficacy often is estimated, in terms of VEs, using a variety of case definitions that correspond to differing levels of severity [7, 15, 26–28], the interpretation of these estimates has been different from ours. The denominator in those analyses is total child-years at risk, as in our estimates of VEs, not children with symptomatic disease and confirmed infection, as in our estimates of VEp. Chang et al. [29] suggest an efficacy measure that is based on the net burden of illness per subject and that takes both incidence and clinical severity into account. However, their measure does not condition on experiencing a confirmed episode of disease, as does ours.

This is an observational study and is therefore susceptible to biases, mainly selection bias, at 2 levels: in the ascertainment of cases of pertussis or in laboratory confirmation of cases. Here, active surveillance with a low threshold for case detection (cough of >7 days' duration) probably allowed us to achieve good ascertainment of cases in vaccinated and in unvaccinated children. Nearly all children had at least 1 laboratory test done, which would also minimize selection bias in biological sampling. Slightly fewer serologic tests were performed among unvaccinated than among vaccinated children. However, rates of isolation of *Bordetella* were higher among unvaccinated children than among vaccinated children with breakthrough cases. Thus, the proportion of cases confirmed only indirectly, by positive results of culture of a sample from a contact, were similar in both groups. This probably indicates that confirmation rates did not differ among groups when both culture and serologic test results are considered. However, the rate of confirmation of pertussis infection might be lower in the vaccinated group. Thus, either the number of severe cases or the total number of cases should be higher than measured. If only the first number is higher among vaccinated children, then VEp would go up. In this case, our estimate of VEp is conservative. If both numbers are higher and to an equal degree, VEp does not change. If, although this is unlikely, more-severe cases were confirmed less often, our estimate is an overestimate. Selection biases are more likely to occur in studies that assess severity among hospitalized children or those who receive care at a clinic or a practitioner's office.

In summary, we studied the efficacy of pertussis vaccination, as it is used in actual practice in many developing countries (a primary series of 3 doses administered in infancy, with no subsequent booster dose), in reducing disease severity. We found that vaccination was effective in reducing the severity of breakthrough illness.

Acknowledgments

We are grateful to the participating children, their mothers, and their families. We are indebted to the team of the Niakhar project at the time of the pertussis clinical trials, in particular to Dr. Francois Simondon (head), Dr. Ablaye Yam (who was in charge of pertussis surveillance), Laurence Chabirand (who was in charge of vaccinations), and Drs. Anouch Chahnazarian and Valérie Delaunay (who were in charge of the demographic registration system). We also thank Drs. Michel Garenne and Peter Aaby (initiators of pertussis surveillance in the area), Drs. Coumba Toure Kane and Souleymane Mboup (University Cheikh Anta Diop, Dakar, Senegal), and Drs. Nicole Guiso and Isabelle Iteman (Institut Pasteur, Paris), who were in charge of biological surveillance and analyses for the pertussis trials.

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