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Clinical Presentation of Pertussis in Unvaccinated and Vaccinated Children in the First Six Years of Life

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ABSTRACT. *Objectives.* **Identifying the determinants of the clinical presentation of pertussis is important for the purposes of diagnosis, therapy, and control and for predicting the disease's clinical course and choosing an appropriate case definition for surveillance. Potential determinants include vaccination status, antibiotic treatment, age at diagnosis, and sex, although the available data are inconsistent. The objective of this study was to compare the clinical course of pertussis in unvaccinated and vaccinated children in a well-defined and strictly studied population and to identify determinants of the disease's clinical presentation.**

Methods. **The clinical presentation of pertussis was studied in children who participated in a randomized, controlled clinical trial of efficacy of acellular pertussis vaccine. The children belonged to the same birth cohort and were followed from infancy to 6 years of age in 3 distinct periods (stages 1, 2, and 3). Children had received 1 of 2 three-component acellular pertussis vaccines produced by 2 manufacturers (diphtheria-tetanus-acellular pertussis from, Chiron Biocine [DTaP CB]; DTaP from SmithKline Beecham [DTaP SB]) or a diphtheria-tetanus vaccine only (DT; Chiron Biocine). Pertussis was confirmed through culture or serology. For each pertussis episode, information was collected on age at onset, sex, type of vaccine received, antibiotic treatment, culture results, duration of cough, spasmodic cough, and other symptoms. The simultaneous effect of potential determinants of clinical presentation of pertussis on the duration of cough and spasmodic cough was studied through analysis of variance models.**

Results. **The analysis was conducted on 788 laboratory-confirmed cases of pertussis. The median duration of cough in DT recipients varied from 52 to 61 days across the 3 stages, whereas the median duration of cough in DTaP recipients varied from 29 to 39 days. The median duration of spasmodic cough varied from 20 to 45 days in DT recipients and from 14 to 29 days in DTaP recipients. The results of the analysis of variance models showed that vaccination against pertussis reduced the length of cough from 3 to 10 days and the length of spasmodic cough from 4 to 8 days. Culture-positive patients had a cough 11 to 22 days longer and a spasmodic cough 12 to 22 days longer than culture-negative patients. Children who received an antibiotic had a duration of cough 6 to 11 days longer and spasmodic cough 4 to 13 days longer than untreated patients. Girls had a duration of spasmodic cough 7 days longer than boys only after 3 years of age. Age was directly related to duration of cough, whereas it was inversely related to duration of spasmodic cough after 3 years of age.**

Conclusions. **Duration of cough can be greatly influenced by vaccination status. A positive culture for *Bordetella pertussis* is more frequently found in patients with long duration of cough, and antibiotic therapy may be a marker of severe disease. Gender may affect the clinical presentation of pertussis only after infancy. Pertussis in older children may be characterized by short duration of spasmodic cough. These results should be taken into account in the clinical evaluation of patients with suspected pertussis. Clinical case definitions for the purpose of surveillance based on the presence of 2 weeks of spasmodic cough may not be appropriate where pertussis vaccination uptake is high.** *Pediatrics* **2003;112: 1069–1075;** ***pertussis, children, clinical presentation, cough, pertussis vaccine.***

ABBREVIATIONS. WHO, World Health Organization; DT, diphtheria-tetanus; DTaP, diphtheria-tetanus-acellular pertussis; CB, Chiron Biocine; SB, Smithkline Beecham; DTP, whole-cell diphtheria-tetanus-pertussis; PT, pertussis toxin; FHA, filamentous hemagglutinin; PRN, pertactin; PCR, polymerase chain reaction; IgG, immunoglobulin G; IgA, immunoglobulin A.

Although mass pertussis vaccination in infancy has led to a decrease in the incidence of the disease in many countries, an increasing number of outbreaks among populations with high vaccination coverage have occurred.[1–3] The reported incidence of pertussis among vaccinated individuals probably represents an underestimation because the clinical presentation of the disease is less severe in immunized individuals than in those who are not vaccinated; thus, the disease is often misdiagnosed.

Identifying the determinants of clinical presentations of the disease thus becomes important in accurately diagnosing pertussis, in addition to providing proper therapy, implementing control measures, and predicting the course of the disease. Although the studies conducted to identify the determinants of the clinical presentation of pertussis are controversial, some common factors have been identified: vaccination status,[4–7] antibiotic treatment,[8] sex,[5] and age at diagnosis.[4,5] Immunized children experience milder pertussis,[4–7] whereas positivity of culture has been reported as a marker of severity of pertussis.[6] Antibiotic treatment is believed to be effective in improving the course of the disease if started early,[8] although some studies have found that treatment has no effect.[9,10] Nonetheless, the disease is often recog-

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nized late, and appropriate antibiotic treatment is consequently begun too late to be effective or to prevent secondary cases.[11] It has been reported that girls have a higher risk of developing severe pertussis compared with boys,[5] and age is inversely related to the severity of the disease.[4,5] The effect of an increased force of infection on the clinical presentation of pertussis during epidemic periods has never been investigated.

Determining the effect of vaccination status and other factors on clinical presentation of pertussis is also important for developing and discussing case definitions for surveillance. For example, surveillance based on the case definition recommended by the World Health Organization (WHO)[12] may miss cases among vaccinated individuals in areas with high vaccination coverage, where atypical or milder cases are likely to be frequent.

The objectives of the present study were to compare the clinical presentation of laboratory-confirmed pertussis in children who had been vaccinated with an acellular pertussis vaccine to that in unvaccinated children and to identify the possible additional determinants of the severity of the disease. We also discuss the implications of the results for clinical case definitions used for surveillance.

METHODS

Study Population and Vaccines

The study population consisted of children who, during the Italian Trial on Acellular Pertussis Vaccines, had received a diagnosis of laboratory-confirmed pertussis. During the trial, children had been randomized to receive 3 doses of a diphtheria-tetanus (DT) vaccine, manufactured by Chiron Biocine (CB), 1 of 2 diphtheria-tetanus-acellular pertussis (DTaP) vaccines, manufactured by Smithkline Beecham (SB) and CB, or a whole-cell diphtheria-tetanus-pertussis (DTP vaccine), manufactured by Connaught. Children were distributed among these 4 vaccine groups in a proportion of 1:3:3:3, respectively. For the present study, we considered only children who had completed the 3 doses of primary immunization (at 2, 4, and 6 months of age) of the DT vaccine or of the same DTaP vaccine.

The trial's original study population consisted of 15 601 children who belonged to the same birth cohort. Girls represented 49.6% of the total population, and the age at enrollment of the children was balanced among the vaccine groups.[13] Children were excluded from the trial when they met any of the following criteria: weight at the time of first vaccination below the third percentile, history of pertussis vaccination, previous illness compatible with pertussis, history of central nervous system disease or damage in the perinatal period, history of convulsions, major congenital abnormalities, renal failure, failure to thrive, or an immunodeficiency.

Both DTaP vaccines included pertussis toxin (PT), filamentous hemagglutinin (FHA) and pertactin (PRN). The DTaP manufactured by SB contains 25 μg of PT inactivated by formalin and glutaraldehyde, 25 μg of FHA, and 8 μg of PRN per dose. The DTaP manufactured by CB contains 5 μg of genetically inactivated PT, 2.5 μg of FHA, and 2.5 μg of PRN.

During the trial, the children were followed for the detection of pertussis during 3 distinct periods that had slightly different study designs (referred to as stages 1, 2, and 3) from 1992 to 1998. Stage 1 was conducted in a double-blind manner and included children from 6 to 24 months of age.[13] Stage 2 was conducted in a partially blinded manner, in that parents were informed of which type of vaccine their child had received (DT, DTP, or DTaP); in this stage children were followed from 25 to 33 months of age.[14] Stage 3 was conducted in an unblinded manner and included children from 34 months to 6 years of age.[15] Because most parents of children who belonged to the original DT group accepted the offer to vaccinate their child against pertussis during stage 2 and were excluded from the study, additional children were recruited for stage 3. Specifically, we recruited children who were identified from the census list as belonging to the same birth cohort and living in the same areas as the trial participants and who had no history of pertussis or pertussis vaccination and no serologic evidence of pertussis.[15] These patients, however, had received 3 doses of DT vaccine during the first year of life according to the Italian regulation.

Surveillance of Pertussis

For all 3 trial stages, specially trained nurses were responsible for the active surveillance of pertussis. Parents were instructed to report to the study nurse any cough episode lasting 7 days or more and to record the clinical characteristics of the cough episodes in a daily diary, which was reviewed and transcribed weekly by the study nurse over the telephone. Once a month, the study nurses also contacted all parents by telephone to ensure that cough episodes had been reported and to encourage reporting. Information on hospitalization was also routinely collected by telephone. If the child was hospitalized for pertussis, then detailed information on the time of hospitalization and complications was collected. For the purposes of this study, we examined only laboratory-confirmed cases of pertussis occurring after the child had received 3 doses of DT or DTaP vaccine.

Laboratory Methods

Cough episodes lasting 7 days or more were investigated for laboratory confirmation of pertussis. A nasopharyngeal aspirate and a capillary blood sample were collected in the acute phase (ie, at cough detection), and a second capillary blood sample was collected 6 to 8 weeks later (ie, in the convalescent phase). Cultures for *Bordetella pertussis* and *B parapertussis* were performed on the nasopharyngeal aspirates, and blood samples were tested for antibodies (immunoglobulin G [IgG] and immunoglobulin A [IgA]) against PT and FHA.[13] When the quantity of serum was sufficient, PT-neutralizing antibodies were measured on Chinese hamster ovary cells.[13] For children who were culture negative and who showed an increase in antibodies against FHA in the convalescent phase, compared with the acute phase, the nasopharyngeal aspirate was subjected to a polymerase chain reaction (PCR) test for *B parapertussis*.

Case Definitions

A laboratory-confirmed case of pertussis was defined as an episode of cough lasting 7 days or more, with at least 1 of the following criteria met: 1) a positive culture (nasopharyngeal aspirate) for *B pertussis*; 2) an increase of at least 100% in IgG or IgA titers against PT in the convalescent-phase serum sample compared with the acute-phase sample; 3) a 4-fold increase in the PT-neutralizing titer in the convalescent-phase serum sample compared with the acute-phase sample; 4) an increase of at least 100% in IgG or IgA titers against FHA in the convalescent-phase serum sample compared with the acute-phase sample plus a negative PCR for *B parapertussis*; and 5) in stage 3 only, an IgG titer against PT in 1 of the 2 serum samples greater than the geometric mean titer calculated on convalescent-phase serum samples from children with a culture-confirmed *B pertussis* infection (calculated for each study group).[13–15]

Symptoms were recorded according to parents' report. Cough was defined as the presence of any cough, whereas spasmodic cough was defined as fits of coughing. Apnea was defined as a posttussive episode of breath spells irrespective of its duration; cyanosis, as occurring on the face, lips, or fingers during cough; and vomiting, as the occurrence of a posttussive episode during the disease.

Children were considered as having been treated with antibiotics when therapy with a macrolide or trimethoprim-sulfamethoxazole was begun within 1 week of the onset of cough and lasted for at least 7 days or when therapy with azithromycin was begun within 1 week and lasted for at least 3 days. All children who did not fulfill this definition were considered untreated.

Statistical Analysis

Demographic information and data on the laboratory diagnosis of pertussis, the duration of symptoms (cough and spasmodic cough, and, in stages 1 and 2 only, apnea, cyanosis, and vomiting),

and antibiotic treatment were collected on standardized forms and entered in an electronic database. Because the study design was different for each of the 3 trial stages, the analysis was conducted separately by stage. Differences in the composition of the study population in terms of sex, age, and culture results by vaccine type and stage were investigated through the χ^2 test, the χ^2 test for trend for ordinal variables, and the median test for continuous variables.

The clinical course of pertussis was described as the proportion of patients with pertussis who experienced specific symptoms, with the median duration of symptoms in days, and with the mean number of spasms per day. The duration of symptoms by type of vaccine was tested at the univariate level through the Kruskall-Wallis test. At the multivariate level, analysis of variance analyses were performed to evaluate the simultaneous effect of sex, age (as a continuous variable), background incidence (as a continuous variable), vaccine type, culture results, and antibiotic treatment on the duration of cough and spasmodic cough. For this purpose, the duration of cough and of spasmodic cough were log-transformed because they were not normally distributed. The background incidence of pertussis in the general population during the study period was derived from routine notifications to the Italian Ministry of Health.[16]

RESULTS

A total of 788 cases of laboratory-confirmed *B pertussis* infection were detected during the 3 trial stages. The median age of these children at pertussis diagnosis varied from 29.7 months for DT recipients to 34.6 months for DTaP CB recipients ($P = .873$). The proportion of girls varied from 49.0% for DT recipients to 51.8% for DTaP CB recipients ($P = .791$). Culture-positive pertussis was more common among the DT recipients than among the DTaP recipients (DT: 61.7%; DTaP SB: 39.6%; DTaP CB: 36.5%; $P < .001$). The proportion of cases observed from July to September, the period in which maximum incidence usually occurs, varied from 28.7% among the DT recipients to 33.8% among the DTaP SB recipients, with no significant differences ($P = .714$).

The characteristics of the study population by stage and vaccine group are reported in Table 1. There was no difference in sex distribution in any of the vaccine groups by stage. The median age of pertussis cases among the DT recipients and that of the DTaP SB recipients both were significantly lower than that of the DTaP CB recipients in stage 1. Culture was more frequently positive in the DT recipients than in the DTaP recipients in all stages. In all vaccine groups, the proportion of children with positive culture progressively decreased from stage 1 to stage 3 ($P < .001$).

TABLE 1. Characteristics of 788 Children With *B pertussis* Infection by Stage

	DT ($N = 261$)	DTaP SB ($N = 278$)	DTaP CB ($N = 249$)
Stage 1			
N	97	89	87
Female sex	51 (52.6%)	51 (57.3%)	48 (55.2%)
Median age (mo)	17.32	17.25	19.54*
Culture positive	76 (78.4%)†	47 (52.8%)	44 (50.6%)
Stage 2			
N	41	55	37
Female sex	23 (56.1%)	26 (47.3%)	19 (51.4%)
Median age (mo)	26.96	27.55	27.45
Culture positive	29 (70.7%)‡	28 (50.9%)	17 (45.9%)
Stage 3			
N	123	134	125
Female sex	54 (43.9%)	66 (49.3%)	62 (49.6%)
Median age (mo)	60.33	56.44	58.92
Culture positive	56 (45.5%)§	30 (24.0%)	30 (24.0%)

* DTaP CB versus DTaP SB and DT; $P = .022$.
† DT versus DTaP SB and DTaP CB; $P < .001$.
‡ DT versus DTaP SB and DTaP CB; $P = .058$.
§ DT versus DTaP SB and DTaP CB; $P = .001$.

Table 2 shows the proportion of children who experienced clinical symptoms and the duration of symptoms by stage and vaccine group. The proportion of children with spasmodic cough was consistently higher among DT recipients than among DTaP recipients in all stages except stage 2, in which DT recipients had spasmodic cough more frequently than DTaP CB recipients only. Furthermore, the proportion of children with apnea, cyanosis, and vomiting was higher in DT recipients compared with DTaP recipients in stage 1 and in stage 2.

Duration of cough and spasmodic cough was notably lower in DTaP recipients in all stages. The range of duration of these symptoms included patients with very short cough or spasmodic cough, especially in DTaP recipients. The mean number of spasms per day was higher for DT recipients in stages 1 and 3 compared with DTaP recipients and increased with age in all groups (stage 1—DTaP SB: 5.2, DTaP CB: 6.1, DT: 10.4 [$P < .01$]; stage 2—DTaP SB: 9.0, DTaP CB: 5.0, DT: 9.1 [$P = .8$]; stage 3—DTaP SB: 16.4, DTaP CB: 17.9, DT: 27.8 [$P < .01$]). Apnea and cyanosis had a similar duration in all vaccine groups in stages 1 and 2, whereas vomiting was notably shorter in DTaP recipients.

Within each vaccine group, the duration of cough remained relatively constant over the 3 stages, whereas the duration of spasmodic cough greatly decreased in stage 3 ($P < .001$). Within each vaccine group, the duration of apnea, cyanosis, and vomiting did not change when comparing stage 1 with stage 2.

Tables 3 and 4 illustrate the independent effect of covariates (vaccine type, culture results, antibiotic treatment, sex, age, and background incidence) on the mean duration of cough (Table 3) and spasmodic cough (Table 4), as determined analysis of variance analyses. The intercept of the analysis of variance models represents the expected mean baseline duration of cough or spasmodic cough with all covariates set to the reference value. The baseline duration varied between 19 and 24 days for cough and between 19 and 23 days for spasmodic cough. Having received a DTaP vaccine was associated with a reduction of up to 10 days for the duration of cough as calculated in stage 1 for DTaP SB and of up to 8 days for the duration of spasmodic cough, as reported in stage 1 for DTaP CB when compared with DT recipients. Receiving the DTaP SB vaccine was associated neither with a significant reduction of cough in stage 2 nor with a significant reduction of spasmodic cough in stages 2 and 3, compared with DT. A positive culture was associated with and increase of 11 to 22 days of duration of a cough and of 12 to 22 days for duration of spasmodic cough, compared with patients with a negative culture. Antibiotic administration was associated with an increase of 5 to 6 days of duration of cough compared with untreated patients. Duration of spasmodic cough was affected by

TABLE 2. Clinical Presentation of Pertussis by Stage and Vaccine Group

	Stage 1			Stage 2			Stage 3		
	%	Median Duration (Days)	Range	%	Median Duration (Days)	Range	%	Median Duration (Days)	Range
DT (N = 261)									
Cough	100	61.0*	16–274	100	60.0*	15–134	100	52.0*	12–220
Spasmodic cough	94.8†	38.5*	2–274	97.6‡	45.0*	4–131	82.9§	20.0*	1–89
Apnea	84.5*	19.0	1–76	73.2§	19.5	1–125	—	—	—
Cyanosis	64.9*	10.0	1–68	51.2§	13.0	1–106	—	—	—
Vomiting	85.6*	10.0*	1–55	75.6‖	14.0*	1–42	—	—	—
DTaP SB (N = 278)									
Cough	100	29.0	7–265	100	39.0	9–232	100	35.0	8–288
Spasmodic cough	84.3	21.0	1–265	90.9	29.0	2–232	72.4	14.0	1–164
Apnea	46.6	12.0	1–79	47.3	14.0	1–54	—	—	—
Cyanosis	30.7	9.0	1–30	21.8	6.5	1–35	—	—	—
Vomiting	55.7	3.0	1–37	70.9	5.0	1–42	—	—	—
DTaP CB (N = 249)									
Cough	100	33.0	7–195	100	31.0	9–145	100	35.0	8–196
Spasmodic cough	83.9	21.0	1–195	81.1	23.5	6–128	64.8	15.0	1–159
Apnea	35.6	9.0	1–84	35.1	10.0	2–35	—	—	—
Cyanosis	20.7	6.5	1–56	27.0	6.0	1–40	—	—	—
Vomiting	57.5	4.0	1–55	54.1	3.5	1–26	—	—	—

* DT versus DTaP SB and DTaP CB; $P < .001$.
† DT versus DTaP SB and DTaP CB; $P = .01$.
‡ DT versus DTaP CB; $P = .02$.
§ DT versus DTaP SB and DTaP CB; $P < .05$.
‖ DT versus DTaP CB; $P = .04$.

TABLE 3. Effect of Covariates on Duration of Cough*

	Variation From Baseline Duration of Cough (Days)	P Value
Stage 1 (R^2 = 0.363)		
Baseline mean duration of cough d; intercept: 24.5	0.0	.000
Vaccine type		
DTaP SB	−10.2	.000
DTaP CB	−9.7	.000
Culture positive	+21.6	.000
Received antibiotic treatment	+6.1	.013
Female sex	+0.6	.738
Age	+0.6	.002
Background incidence	−0.8	.495
Stage 2 (R^2 = 0.337)		
Baseline mean duration of cough d; intercept): 19.0	0.0	.000
Vaccine type		
DTaP SB	−3.5	.112
DTaP CB	−6.5	.003
Culture positive	+15.8	.000
Received antibiotic treatment	+6.0	.039
Female sex	−1.9	.311
Age	+0.4	.272
Background incidence	+2.1	.412
Stage 3 (R^2 = 0.164)		
Baseline mean duration of cough d; intercept): 24.4	0.0	.000
Vaccine type		
DTaP SB	−5.6	.002
DTaP CB	−5.6	.002
Culture positive	+10.9	.000
Received antibiotic treatment	+5.0	.030
Female sex	+1.1	.516
Age	+0.2	.046
Background incidence	+3.3	.212

* Reference categories for covariates: sex: male; vaccine: DT; culture positive: no; antibiotic treatment: no.

antibiotic treatment only in stages 1 and 2 with an increase in duration of 6 to 13 days.

Female sex affected only the duration of spasmodic cough in stage 3, which was 7 days longer compared with boys. Age was directly related to the duration of cough in stages 1 and 3 (0.2–0.6 days per month of age), whereas it was inversely related to the duration of spasmodic cough in stage 3 (0.3 days per

TABLE 4. Effect of Covariates on Duration of Spasmodic Cough*

	Variation From Baseline Duration of Spasmodic Cough (Days)	*P* Value
Stage 1 ($R^2 = 0.182$)		
Baseline duration of spasmodic cough (d; intercept): 19.0	0.0	.000
Vaccine type		
DTaP SB	−7.4	.001
DTaP CB	−7.6	.001
Culture positive	+13.5	.000
Received antibiotic treatment	+6.4	.033
Female sex	+3.0	.222
Age	+0.2	.396
Background incidence	−0.6	.653
Stage 2 ($R^2 = 0.261$)		
Baseline duration of spasmodic cough (d; intercept): 22.2	0.0	.000
Vaccine type		
DTaP SB	−4.0	.233
DTaP CB	−7.0	.043
Culture positive	+22.2	.000
Received antibiotic treatment	+13.5	.005
Female sex	−1.4	.641
Age	−0.1	.837
Background incidence	+2.5	.527
Stage 3 ($R^2 = 0.098$)		
Baseline duration of spasmodic cough (d; intercept): 23.3	0.0	.000
Vaccine type		
DTaP SB	−4.7	.122
DTaP CB	−7.0	.020
Culture positive	+12.0	.001
Received antibiotic treatment	+4.2	.272
Female sex	+7.1	.026
Age	−0.3	.028
Background incidence	+6.5	.161

* Reference categories for covariates: sex: male; vaccine: DT; culture positive: no; antibiotic treatment: no.

month). No associations were found between background pertussis incidence and duration of cough or spasmodic cough.

Hospitalizations and Complications

During the whole study period, the hospitalization rate, which also includes visits to the emergency department, was 1.8%. A total of 11 hospitalizations and 3 emergency department visits were reported: 3 hospitalizations and 2 emergency department visits among the DT recipients, 4 hospitalizations and 1 emergency department visit among the DTaP SB recipients, and 4 hospitalizations among the DTaP CB recipients. The length of hospitalization ranged from 2 to 10 days. Of the 14 hospitalizations and visits, 8 were reported for children <36 months of age. There was no difference in the number of hospitalizations and visits by vaccine group.

The most frequent reason for hospital admittance (ie, hospitalizations and emergency department visits) was severe cough. Two children received a diagnosis of bronchopneumonia; these children were 42 and 43 months of age, and both of them belonged to the DTaP SB group. One child received a diagnosis of dehydration; the child was 44 months of age and belonged to the DTaP CB group. One child experienced seizures during pertussis but was not hospitalized and recovered without sequelae; the child was 24 months of age and belonged to the DT group. No deaths caused by pertussis were reported.

DISCUSSION

Although previous works have reported on the clinical characteristics of pertussis at various ages, little research has compared the symptoms in vaccinated children with those in unvaccinated children. Moreover, the data on symptoms have traditionally been provided by observational studies in which a multivariate approach was not applied for identifying the determinants of severity and controlling for confounding.[5–8,10] The existing studies on symptoms differ in terms of the composition, size, and vaccination status of the study population and the method of diagnosis.[10]

The present study provides the only available results on the clinical course of pertussis in a well-defined large population of children who belonged to the same birth cohort and were followed strictly for the onset of the disease. These results can be considered accurate, in that the number of cases detected was high, all cases were laboratory confirmed, and case surveillance was actively conducted over the entire study period. Children belonged to a randomized cohort that also included a DT group and allowed a valid comparison between vaccinated and unvaccinated children. Moreover, the multivar-

iate approach allowed us to determine the independent effect of each single covariate on the duration of cough and spasmodic cough.

The results of this study confirm that vaccination status significantly changes the clinical presentation of disease and that pertussis is more severe in unvaccinated children.[5,7] In fact, the DT recipients more frequently expressed the full spectrum of typical pertussis symptoms, and the duration of these symptoms was greater than in vaccinated children, particularly for spasmodic cough, although it must be noted that the duration of cough and spasmodic cough can vary greatly even in vaccinated children. The effect of the 2 three-component acellular vaccines in shortening the duration of cough and spasmodic cough varied in a limited range, a finding that is consistent with the efficacy estimated for the 2 vaccines during the 3 trial stages.[13–15] The lack of a significant effect in reducing the duration of cough and spasmodic cough for the DTaP SB vaccine in stage 2 may be attributable to the short study period and the low number of cases observed in this stage. However, a lack of effect in reducing the duration of spasmodic cough was observed also in stage 3, suggesting that this vaccine may have a lower impact on clinical presentation of pertussis in the long-term.

It can be speculated that pertussis is less severe in vaccinated children because the acellular vaccines may interfere with the pathophysiology of the disease. However, it is not known whether the extent of this interference varies with the particular composition of the vaccine used. Besides clinical efficacy, no study has reported on the effect of different acellular vaccines on the clinical presentation of pertussis. A comparison of the severity of pertussis in children vaccinated with acellular vaccines with different numbers of components would help to clarify the role that single components play in prevention.

Culture-confirmed pertussis was more frequent among the DT recipients, and, in all vaccine groups, it was related to a longer duration of symptoms, a finding that is consistent with reports of a more severe clinical presentation among individuals with culture-confirmed disease.[6,17] A positive culture may be a marker of longer delays in the clearance of *B pertussis* from the respiratory epithelium and of more severe damage, which would result in a more severe clinical presentation.

It has been reported that erythromycin reduces the severity and duration of disease when started early.[8] We used a stringent definition of antibiotic treatment and a duration of treatment of 7 days based on the observation that this course of therapy is comparable to 14 days.[18] Although this study was not designed specifically for estimating antibiotic clinical efficacy, antibiotic treatment was found to be a marker of severe disease, a finding that is similar to the results of previous studies.[10] Despite recommendations that treatment be started early for improving the clinical course of the disease, most trials on the efficacy of antibiotics in patients with pertussis have focused on the eradication of *B pertussis* rather than on the duration of symptoms.[19] This issue probably deserves more attention in future studies.

Although pertussis disease is commonly considered to be more frequent and more severe among girls,[5] in our study, the proportion of cases involving girls did not exceed that of boys, and only the duration of spasmodic cough in stage 3 was longer among girls. These findings support the hypothesis that sex may influence the clinical presentation of disease only after 3 years of age.[10]

The findings that the duration of cough did not vary within any of the vaccine groups when comparing the 3 stages and that age was directly related to the duration of cough in stages 1 and 3 do not support the concept that the duration of disease decreases with age, particularly in immunized children.[4,5] Conversely, the duration of spasmodic cough sharply decreased in all vaccine groups, and age was inversely related to the duration of spasmodic cough in stage 3 (ie, after 33 months of age). Therefore, our results suggest that the duration of symptoms of pertussis is stable in the first 3 years of life, whereas the duration of spasmodic cough is shorter after this age.

Background incidence was included among the covariates for the duration of cough and spasmodic cough because we presumed that the force of infection, which increases during epidemic periods, might have influenced the clinical presentation. However, our results showed that the clinical presentation of pertussis did not vary with background incidence.

Besides the typical symptoms, complications and hospitalizations were rare in our cohort. Although this finding probably reflects the selection of patients for participation in the trial, a study conducted in the United Kingdom also suggests that the disease is much less severe than suggested by textbook descriptions or parents' fears.[8]

A small proportion of children, although having received a diagnosis of pertussis infection, presented with short cough or without spasmodic cough. The number of children without spasmodic cough increased among vaccinated children and older children. Other studies have reported that the disease is often atypical and sometimes presents only as a protracted, nondistinctive cough, especially in adolescents and adults[17] and immunized individuals.[7] This observation has a substantial impact for surveillance activities. Because the recommended WHO case definition for surveillance includes 2 weeks of spasmodic cough as a clinical hallmark,[12] the impact of disease may be selectively underestimated in vaccinated children and in older age groups. In fact, the incidence of pertussis is largely underestimated worldwide,[20,21] and in populations with high vaccination coverage, a more sensitive case definition should be adopted. The appropriateness of the case definition is also important in calculating vaccine efficacy in clinical trials of pertussis vaccines.[22] In this respect, estimates of efficacy based on case definitions that include a shorter duration of cough or that do not consider spasmodic cough may be more informative than estimates based on the WHO case definition. This was the case in the Italian trial, in

which the efficacy of vaccines was also calculated on the basis of milder case definitions.[13]

To date, many surveillance systems have relied on the culture of *B pertussis* for qualifying a laboratory-confirmed case. However, when conducting surveillance, case definitions that include culture as the only criterion for laboratory confirmation may result in more severe cases being selected, especially among unvaccinated individuals. Moreover, the culture may be negative after antibiotic treatment has started or if the culture was performed late in the course of illness.[4] More sensitive laboratory tests for the diagnosis of pertussis, including PCR and serology, should be considered for surveillance purposes in populations with high vaccination coverage.[23]

CONCLUSIONS

Children with prolonged cough should always be considered for the diagnosis of pertussis, even when appropriately immunized. Pertussis is milder after 3 years of age. Despite the uncertain role of antibiotic treatment in improving the course of pertussis, failure to diagnose the disease may result in antibiotic treatment being started late and in an increased potential for secondary transmission.[24] The WHO case definition for pertussis surveillance may not be sensitive in immunized children and toddlers.

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Clinical Presentation of Pertussis in Unvaccinated and Vaccinated Children in the First Six Years of Life

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