Clinical Findings in *Bordetella pertussis* Infections: Results of a Prospective Multicenter Surveillance Study

Ulrich Heininger, MD*; Kerstin Klich, MD*; Klemens Stehr, MD*; and James D. Cherry, MD‡

ABSTRACT. *Objective.* **To study the clinical presentation of culture-confirmed pertussis in children and their contacts with cough illnesses in an outpatient setting.**

Methodology. **In conjunction with a large pertussis vaccine efficacy trial in Germany, a central laboratory to isolate *Bordetella* species from nasopharyngeal specimens was established in Erlangen in October 1990. Pediatricians in private practices in southern Germany, the Saar region, and Berlin were encouraged to obtain nasopharyngeal specimens and clinical characteristics from patients with cough illnesses 7 days' duration. *Bordetella* species were isolated by use of calcium alginate swabs, Regan–Lowe agar, and modified Stainer–Scholte broth. Clinical characteristics were determined by initial and follow-up questionnaires.**

Results. **From October 1990 to September 1996, 20 972 specimens were submitted, and *B pertussis* was isolated in 2592 instances (12.4%). Of the culture-proven cases, 50.7% were female, and the age range was 6 days to 41 years, with a mean and median of 4.3 years and 4.1 years, respectively. The following characteristics were noted. Only 4% of the patients had received pertussis vaccine. Of unvaccinated patients, 90.2% had paroxysmal cough, 78.9% demonstrated whooping, and 53.3% presented with posttussive vomiting; 5.7% had fever 38°C. The duration of cough was 4 weeks in 37.9% and 3 weeks in 17.4%. Leukocytosis and lymphocytosis (values above the age-specific mean) were observed in 71.9% and 75.9% of unvaccinated patients, respectively. The overall complication rate was 5.8%, and pneumonia (29%) was the most frequent complication. In infants <6 months of age, the rate of complications was 23.8%. One death in a 7-month-old infant occurred.**

Conclusions. **Typical symptoms of pertussis were observed in the great majority of patients regardless of age group. However, the duration of cough was surprisingly short in one sixth of the patients. These short illness cases would not be classified as pertussis according to the World Health Organization clinical case definition, which requires 21 days of spasmodic cough. *Pediatrics* 1997;100(6). URL: http://www.pediatrics.org/cgi/content/full/100/6/e10; *Bordetella pertussis, surveillance, symptoms, white blood cells.***

From *Universitätsklinik mit Poliklinik für Kinder und Jugendliche, Erlangen, Germany; and ‡Department of Pediatrics, University of California Los Angeles School of Medicine, Los Angeles, California.

This work includes data from Kerstin Klich's medical thesis (University of Erlangen, Erlangen, Germany).

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Reprint requests to (J.D.C.) Division of Pediatric Infectious Diseases, UCLA School of Medicine, 10833 Le Conte Ave, Los Angeles, CA 90095-1752.

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ABBREVIATIONS. NPS, nasopharyngeal specimen(s); WBC, white blood cell(s); CI, confidence interval; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization.

During the last two decades, *Bordetella pertussis* infections have been endemic and epidemic in the former West Germany because of low immunization rates varying from 0% in northern parts of Germany up to 30% in some southern areas.[1,2] This prevalence served as the background for a large German pertussis vaccine efficacy trial initiated in 1991. As a support service for this trial, a central laboratory was established at the Universitätsklinik für Kinder und Jugendliche in Erlangen, and pediatricians in private practices were encouraged to collect nasopharyngeal specimens (NPS) and to obtain initial and follow-up information from all children who presented with cough illnesses.[3]

In this paper, we report clinical manifestations of *B pertussis* infections noted during 6 years of prospective surveillance. The data are unique in that they were obtained in a standardized manner from 2592 outpatients, and all patients had culture-confirmed *B pertussis* infections. Early results from a small subset of children were published previously.[3]

PATIENTS AND METHODS

Participating Physicians

Starting in October 1990, material for NPS collection was offered to interested pediatricians in southern Germany, the Saar region, and Berlin. They were instructed to take an NPS from all patients with a cough illness of ≥7 days' duration, irrespective of a clinical suspicion of pertussis. All NPS were accompanied by a questionnaire.

Questionnaires

From October 1990 to March 1991, questionnaires were obtained at the time of NPS collection and included information on name and date of birth of the patient, date of specimen collection, and duration of cough.

In April 1991, the initial questionnaires were modified and, in addition, follow-up (6 to 8 weeks later) information was requested on each patient. Questions on characteristics of cough, including paroxysmal and, since May 1992, posttussive vomiting; number of pertussis vaccinations; antibiotic pretreatment; body temperature; white blood cell (WBC) count; and contact with a patient with pertussis. Physicians' clinical diagnosis as possible, probable, or definite pertussis was added to the initial questionnaire. Information requested on the follow-up questionnaire comprised total duration of cough; occurrence of paroxysms and whoop; occurrence of complications; and physicians' final clinical diagnosis as unlikely, possible, probable, or definite pertussis.

Specimen Collection and Laboratory Methods

Specimen collection and laboratory methods have been described previously.[3] Briefly, NPS were collected with calcium alginate swabs, placed into half-strength Regan–Lowe transport medium, and preincubated overnight at 37°C before shipment to our laboratory by regular mail. On arrival in our laboratory, the swab was first streaked onto a Regan–Lowe agar plate[4] and then shaken for 15 seconds in modified Stainer–Scholte broth.[5] Cultures were incubated at 37°C. After 48 hours, a fraction of the Stainer–Scholte broth and the original transport medium were streaked onto half of a second Regan–Lowe agar plate and incubated together with the first plate for another 5 days. Plates were inspected daily excluding Sundays, and suspicious colonies were identified as *B pertussis* or *B parapertussis* by oxidase reaction and specific fluorescent antibodies (Difco Laboratories, Detroit, MI).

Data Management and Statistics

All data were entered into a Lotus 1–2–3 database and double-checked for correctness. Calculations and statistical analyses were performed with Superior Performing Software System (SPSS, Chicago, IL). The χ^2 test was used to compare percentages. One-way analysis of variance was used to compare leukocyte and lymphocyte counts in blood specimens from patients and controls. Controls were 98 patients with cough illnesses and negative *B pertussis* cultures and a final clinical diagnosis by the physician of definitely not pertussis.

RESULTS

From October 1990 to September 1996, 20 972 NPS from patients seen in 292 physicians' offices were received. *B pertussis* and *B parapertussis* were isolated in 2592 (12.4%) and 150 (0.7%) instances, respectively. Our findings in patients with *B parapertussis* infections have been published previously[6]; thus, the analyses in this report are restricted to patients with *B pertussis* infection. All 2592 specimens with subsequent isolation of *B pertussis* were accompanied by an initial questionnaire, and 1860 (72%) follow-up questionnaires were received.

A comparison of characteristics at initial presentation in children with and without a follow-up questionnaire was performed. A higher percentage of children for whom follow-up information was not provided presented with cough of >2 weeks' duration at the time of NPS collection, compared with children for whom a follow-up questionnaire was received (25.0% vs 18.6%; $P = .001$). Additional evidence of a more advanced pertussis illness at initial presentation in those children without follow-up information was found by comparing the rates of paroxysmal cough (14.7% vs 9.9%; $P = .17$), posttussive vomiting (58.0% vs 52.0%; $P = .07$), and initial diagnosis of probable or definite pertussis (56.2% vs 50.9%; $P = .03$). When the comparison between these two groups was restricted to children with ≤2 weeks of cough at the initial presentation, no difference in severity of illness was detected between children with and without follow-up information.

Because the questionnaires were not always completely filled out, denominators differ in the separate analyses.

Age, Gender, and Season

Of 2493 patients, 1263 (50.7%) were female. The mean age was 4.3 years (range, 6 days to 41 years), with a median of 4.1 years. A total of 80% of the patients were <6 years of age. In the process of evaluating children with cough illnesses, on occasion the pediatricians also collected NPS from the accompanying adults if they had cough illnesses. A total of 18 cases in adults were identified.

Despite pronounced variability from month to month (range, 0 to 98 cases) during our 6-year study, cases of culture confirmed pertussis occurred with equal frequency during the warm season from April to September (47.2%) and during the colder season from October to March (52.8%). The numbers of specimens and isolation rates of *B pertussis* per year were as follows: 1991, 3402 (*B pertussis*, 474 [14%]); 1992, 6408 (828 [13%]); 1993, 5215 (480 [9%]); 1994, 3990 (505 [13%]). After completion of the active follow-up of the pertussis vaccine efficacy trial in December 1994, the number of specimens sent to our laboratory decreased to 1127 (*B pertussis*, 140 = 12%) in 1995 and 576 (81 = 14%) in 1996.

Immunization History

The great majority of patients with immunization records (2137 of 2238 [95.5%]) had not received pertussis vaccine. Only 27 individuals (1.2%) were appropriately immunized with three doses (<18 months of age; n = 18) or four doses (≥18 months of age; n = 9) of pertussis vaccine at the time they contracted the illness; 65 patients (2.9%) had received one or two immunizations. Of those patients with pertussis despite four doses of vaccine, 67% were older than 6 years.

To avoid bias caused by the influence of pertussis immunization on severity of symptoms, the following analyses were restricted to those 2137 patients who had not received any pertussis vaccine.

Clinical Findings

Selected initial and follow-up characteristics of pertussis by age group are presented in Table 1. None of the analyses showed any significant difference by gender (data not shown). At the time of the NPS collection, 1623 (79.4%) patients had coughed for <2 weeks. Yet of this group, 1206 (81.5%) had already experienced paroxysms and 538 (49.6%) complained of posttussive vomiting. This led to an initial clinical diagnosis of probable or definite pertussis in 780 (51.3%) patients. Because the time point of initial presentation of a patient (ie, initial duration of cough) did not correlate with the severity of illness (as measured by the total duration of cough; correlation coefficient = 0.18), initial questionnaire data from all patients were pooled for analysis. Overall, on initial presentation 82.4% of the patients had paroxysmal cough that was accompanied by posttussive vomiting in 53.3%. A body temperature ≥37°C was noted in 5.7%, with highest rates in children 6 months to 2 years of age (12%) and the lowest rate in individuals >9 years of age (1.6%). At the time of NPS collection, the illness was thought to be probably or definitely pertussis in 52.8% of patients.

Follow-up information revealed that the total duration of cough was ≤3 weeks in 270 (17.4%) and ≤4 weeks in 586 (37.9%) of 1548 patients, respectively. However, cough had been paroxysmal in 90.2%, and whooping had been observed in 78.9%. The final clinical diagnosis was probable or definite pertussis

TABLE 1. Percent Occurrence of Selected Findings in Unvaccinated Patients With *Bordetella pertussis* Infections by Age Group as Reported in Initial and Follow-up Questionnaires

	Age										
	<6 Months	6–12 Months	1–2 Years	2–3 Years	3–4 Years	4–5 Years	5–6 Years	6–9 Years	>9 Years	Total*	
(N) Characteristics	(101) % pos	(84 % pos	(202) % pos	(280) % pos	(341) % pos	(383) % pos	(314) % pos	(338) % pos	(87) % pos	(2135) % pos	N With Data Avaliable
Initial											
Cough ≤2 wk	86.2	84.0	73.8	85.8	78.2	78.2	80.2	76.4	76.8	79.4	2045
Paroxysmal cough	89.2	81.8	77.7	79.5	80.8	84.3	82.4	87.6	78.8	82.4	1948
Vomiting	58.6	47.6	60.0	58.4	49.3	52.7	52.8	54.1	44.3	53.3	1390
Temperature ≥38°C	4.5	11.2	12.6	5.6	5.2	4.3	4.1	5.6	1.6	5.7	1526
Probable or definite pertussis†	69.6	65.4	61.8	54.8	51.7	50.1	46.9	49.5	43.5	52.8	1998
Follow-up											
Cough >4 wk	70.7	62.3	62.7	63.5	57.4	60.1	64.4	63.2	64.5	62.1	1546
Paroxysmal cough	92.6	92.7	92.3	90.2	89.3	88.9	92.0	90.3	84.8	90.2	1604
Whoop	69.1	91.7	80.6	82.8	83.7	78.8	74.5	77.4	66.1	78.9	1378
Probable or definite pertussis†	100	100	97.2	98.0	97.9	95.3	97.1	97.0	98.4	97.3	1574

* Includes 5 patients with unknown age.
† Physician's clinical diagnosis.

in 97.3%. In 3 of 1574 (0.2%) patients, the clinical diagnosis was thought not to be pertussis. Two of these patients had no cough at all, and one child coughed for only 3 days without paroxysms or whooping. The 2 patients with asymptomatic infections had a household contact to a symptomatic case. Interestingly, age had no apparent influence on the occurrence of characteristic symptoms of pertussis such as paroxysmal cough, whooping, or posttussive vomiting, as demonstrated by similar percent values across the different age groups in Table 1.

Antibiotic Use

Specific data on the use of antibiotics before collection of the NPS were requested. Antibiotic treatment had been given to 130 of 1656 (7.9%) patients. In 111 (85%) instances, erythromycin had been used. Patients who had received erythromycin were compared with those without previous antibiotic treatment. Although their mean age was similar (3.9 years vs 4.1 years; $P = .46$), more children with erythromycin use before NPS collection already had a prolonged illness, compared with those without any antibiotics (cough >14 days, 40.2% vs 19.3%; $P < .0001$). When we compared severity of illness as measured by data provided in follow-up questionnaires, no differences were found between these two groups (data not shown). We hypothesized that this was attributable to the rather late initiation of erythromycin treatment in 40.2% of those who received the drug. To analyze further this hypothesis, the outcome of illness was compared between patients with early and late start of erythromycin treatment (cough ≤14 days' duration versus cough >14 days' duration). Mean age was comparable between these two subsets of patients (3.8 years vs 4.5 years; $P = .3$). However, patients with early initiation of erythromycin treatment tended to have shorter illnesses (≤4 weeks, 45.9% vs 25.9%; $P = .08$ and ≤3 weeks, 22.2% vs 14.3%; $P = .32$) and were less likely to have paroxysmal cough (81.5% vs 92.3%; $P = .12$) than those with late onset of treatment.

Complications

Complications were observed in 95 of 1640 (5.8%) patients (Table 2). They were significantly more frequent in infants ≤6 months of age than in patients >6 months of age (23.8% vs 5.1%; $P < .001$). Most common complications were pneumonia (29.5%) and apnea (12.6%). Of all infants ≤6 months of age, 3.2% and 15.9% were reported to have pneumonia and apnea, compared with 1.6% and 0.1% in patients >6 months of age, respectively. There were no seizures reported in this study; however, one 4-month-old infant required several weeks of ventilatory support after cardiopulmonary failure, and one death occurred in a 7-month-old appearing as a sudden infant death.[7] Hospitalization after initial outpatient evaluation was not assessed systematically in this study.

Leukocytosis and Lymphocytosis

In 840 unimmunized patients, a WBC count was performed on the same day the NPS was collected, and in 482 instances, leukocytes were differentiated. The WBC counts of 98 patients with cough illnesses negative for *B pertussis* and a final clinical diagnosis of definitely not pertussis were used as controls.

Patients and controls were comparable in mean age (4.0 years in both groups) and mean duration of cough at the time of the WBC count (12.6 days vs 11.9 days; $P = .92$). Moreover, the mean duration of cough at the time of the WBC count did not differ between individuals with high leukocyte or lymphocyte values (above the age-specific upper limit of the 95% confidence interval [CI] for the mean[8]) and those with values within the normal range (13.0 days vs 12.3 days; $P = .23$ for leukocytes and $P = .34$ for lymphocytes).

Leukocyte and lymphocyte mean and median val-

TABLE 2. Complications in Unvaccinated Patients With *Bordetella pertussis* Infections by Age Group as Reported in Follow-up Questionnaires

Complication	Age					
	<6 Months (n = 63) n (%)	6–12 Months (n = 59) n (%)	1–4 Years (n = 610) n (%)	4–9 Years (n = 846) n (%)	>9 Years (n = 62) n (%)	Total (n = 1640) n (%)
Pneumonia	2 (3.2)	—	8 (1.3)	18 (2.1)	—	28 (1.7)
Apnea/cyanosis	10 (15.9)	1 (1.7)	—	1 (0.1)	—	12 (0.7)
Otitis media	—	—	6 (0.9)	4 (0.5)	—	10 (0.6)
Poor feeding/severe vomiting	2 (3.2)	—	2 (0.3)	2 (0.2)	1 (1.6)	7 (0.4)
Cardiopulmonary failure	1 (1.6)	—	—	—	—	1 (0.1)
Death	—	1 (1.7)	—	—	—	1 (0.1)
Other*	—	1 (1.7)	5 (0.8)	15 (1.8)	—	21 (1.3)
Unspecified	—	—	8 (1.3)	5 (0.6)	2 (3.2)	15 (0.9)
Any	15 (23.8)	3 (5.1)	29 (4.8)	45 (5.3)	3 (4.8)	95 (5.8)

* Includes cases of epistaxis, inguinal hernia, excessive paroxysms, and bronchitis.

ues of patients and controls in different age groups are presented in Tables 3 and 4, respectively. Several findings are of interest. Of the patients, 71.9% and 75.9% had leukocyte and lymphocyte values, respectively, above the mean compared with 38.5% and 37.5% of controls. However, only 29.9% and 34.9% of patients had significant leukocytosis and lymphocytosis (values above the upper limit of the 95% CI of the age-specific mean) at the time they were seen by their physicians for NPS collection. The rates for controls were 2.0% and 10%, respectively. In this analysis, in which age-specific norm values were used to compare leukocyte and lymphocyte values in patients and controls, the rates of leukocytosis and lymphocytosis did not appear to be dependent on age.

DISCUSSION

Despite significant morbidity attributable to infection with *B pertussis* in many countries, only a small number of reports that describe the findings and the course of the illness in a substantial number of patients have been published. The largest studies reported during the last 2 decades are summarized in Table 5. They differ with respect to number and vaccination status of patients, method of diagnosis, and the population studied. In comparison with these studies, our data have several advantages. They were prospectively collected, ie, the physician did not know the patient had pertussis when the initial questionnaire was completed; all patients presented to their primary care physicians; all cough illnesses with a duration of ≥7 days irrespective of a clinical suspicion as being pertussis were studied; all cases of pertussis were confirmed by culture, and 95.5% occurred in unvaccinated patients. In contrast, for example, the large series of cases reported by the US Centers for Disease Control (CDC) is based on all cases notified by state and local health departments between 1980 and 1989.[9] It should be noted that 42.6% of all patients reported in the CDC study were hospitalized. Therefore, that report likely reflects

TABLE 3. Leukocyte Values* in 840 Unvaccinated Patients With Culture-proven *Bordetella pertussis* Infection Compared With 98 Unvaccinated Controls With Other Cough Illnesses

	Age Groups								
	<6 Months	6–12 Months	1–2 Years	2–4 Years	4–6 Years	6–8 Years	8–10 Years	10–16 Years	Total
95% UL of mean†	17.5	17.5	17.0	15.5	14.5	13.5	13.5	13.0	—
Patients									
N	53	29	94	240	261	99	47	17	840
Mean	15.1	17.1	15.8	13.6	12.9	12.2	10.6	8.5	—
(95% CI)	(12.9–17.3)	(13.0–21.1)	(14.1–17.4)	(12.8–14.5)	(11.9–13.8)	(11.2–13.1)	(9.6–11.6)	(7.0–10.0)	
Median	13.2	14.5	14.0	12.1	11.0	11.5	9.5	8.2	—
Percent above normal mean	61.4	65.5	76.6	72.9	72.4	75.8	68.1	58.8	71.9
95% UL of mean†	26.4	37.9	33.0	29.2	28.0	36.4	21.3	35.3	29.9
Controls									
N	7	5	11	28	31	9	3	4	98
Mean	8.4	8.6	11.7	8.4	8.2	8.4	7.6	6.7	—
(95% CI)	(4.1–12.7)	(6.8–10.5)	(9.0–14.5)	(7.3–9.4)	(7.3–9.0)	(5.8–11.0)	(0–19.0)	(1.3–12.2)	
Median	9.4	8.8	12.4	8.4	8.5	7.1	7.2	7.1	—
Percent above normal mean	29	0	50	32	42	33	33	25	38.5
95% UL of mean†	0	0	9	0	0	11	0	0	2.0
P values‡	.04	.09	.10	<.001	<.001	.03	.17	.3	<.001

* $\times 10^3$ per μL.
† UL, Upper limit; reference 8.
‡ Mean of patients controls.

TABLE 4. Lymphocyte Values* in 482 Unvaccinated Patients With Culture-proven *Bordetella pertussis* Infection Compared With 40 Unvaccinated Controls With Other Cough Illnesses

	Age Groups								
	<6 Months	6–12 Months	1–2 Years	2–4 Years	4–6 Years	6–8 Years	8–10 Years	10–16 Years	Total
95% UL of mean†	13.5	10.5	9.5	8.0	7.0	6.8	6.5	5.2	—
Patients									
N	31	15	53	133	151	58	27	14	482
Mean	12.2	12.2	11.1	8.0	7.3	6.2	5.2	3.7	—
(95% CI)	(9.7–14.8)	(5.5–18.8)	(9.2–12.9)	(7.1–9.0)	(6.4–8.2)	(5.4–7.0)	(4.4–6.1)	(2.9–4.4)	
Median	10.8	9.5	9.0	6.7	5.9	5.3	4.7	3.5	—
Percent above mean	74.2	80.0	79.2	66.2	78.8	82.8	92.6	64.3	75.9
95% UL of mean†	38.7	26.7	41.5	36.1	33.8	37.9	22.2	21.4	34.9
Controls									
N	2	2	6	14	9	4	1	2	40
Mean	1.4	4.4	7.3	4.9	4.0	3.8	3.5	2.8	—
(95% CI)	(0–5.1)	(0.8–31.8)	(5.0–9.7)	(3.7–6.1)	(2.2–5.8)	(1.3–6.4)	(0–14.2)	(0–25.0)	
Median	1.4	4.4	6.7	4.7	3.9	3.3	—	2.8	—
Percent above mean	0	0	50	43	33	50	0	50	37.5
95% UL of mean†	0	0	33	7	11	0	0	0	10.0
P values‡	.04	.39	.19	.04	.09	.13	.44	.46	<.001

* $\times 10^3$ per μL.
† UL, Upper limit; reference 8.
‡ Mean of patients controls.

TABLE 5. Major Studies During the Last Two Decades Reporting Clinical Findings of *Bordetella pertussis* Infection

Study Region	Period	Design	Population	Cases (n)	Confirmation of Diagnosis (%)		Rate Vaccinated Appropriate for Age (%)
Nottingham (UK)[13]	1977–1992	Prospective	Outpatients	500	Culture:	20	40
					Clinical:	80	
West Glamorgan (UK)[27]	1977–1979	Prospective	Outpatients	2295	Culture:	39	29
					Clinical:	61	
United States[9]	1980–1989	Prospective	Notifications to CDC	27 826	Culture/DFA:	53	36*
					Clinical:	47	
Toronto (Canada)[18]	1980–1990	Retrospective	Outpatients (referred to hospital)	975	Culture/DFA:	100	75
Sweden[14]	1981–1983	Retrospective	Hospitalized patients	2282	Culture:	40	<10†
					Serology:	6	
					Clinical:	54	
Nova Scotia (Canada)[12]	1985–1987	Prospective	Outpatients	526	Culture:	21	91
					Serology:	11	
					Clinical:	68	

* In children 4 months to 3 years of age.
† Estimated.

more severe illness and not the general overall manifestations of *B pertussis* infections.

It has been shown previously that with the exception of infants, pertussis more frequently affects females than males and that this female preponderance increases with age.[10] In England and Wales between 1975 and 1979, the percentages of females among notified cases of pertussis were 49%, 52% to 53%, and 64% for children <1 year, 1 to 14 years, and ≥15 years of age, respectively.[11] Although Halperin et al[12] and Jenkinson[13] confirmed this finding, our results and other recent studies[9,14,15] showed an even distribution of pertussis between both genders in children. Data from the CDC revealed that up to the age of 15 years, a similar number of boys and girls (50% to 51%) had pertussis, whereas a female preponderance (55% to 69%) was noted in older age groups. This finding could be attributable to more severe and, hence, more reported illnesses in females >15 years of age. Alternatively, babysitting and other social contacts with younger children are generally more frequent for teen-age girls compared with boys, and this could also result in a higher rate of pertussis in females.

The age distribution of our patients with a peak in preschool children is typical for a primarily unvaccinated population.[14–16] In contrast, widespread immunization results in a relative increase of cases in infants, adolescents, and adults.[16,17] Different seasonal patterns for the incidence of pertussis have

been described in the recent literature.[9,12,18] However, we did not note a difference in the incidence of *B pertussis* infections during the colder or warmer seasons in our large series of cases.

The data collected in this study allow a precise description of selected aspects of pertussis as they occur in unvaccinated children. Clinical characteristics of the cough episodes were obtained at two time points: on the day the NPS was taken and 6 to 8 weeks later. At the time of the first assessment, 82.4% of patients had paroxysmal cough, and the majority also had posttussive vomiting, whereas only 5.7% had fever ≥38°C. In spite of the high prevalence of paroxysmal cough and posttussive vomiting, almost half of the patients were not initially considered to be probably or definitely pertussis by the treating physicians. Because pertussis has been highly endemic and epidemic in Germany during the last 2 decades and thus pediatricians are familiar with the typical illness, this is an interesting finding. It suggests that what was reported to be paroxysmal cough in the early stage of the illness was frequently not sufficiently different from the cough in other illnesses to lead the physician to a clinical diagnosis of pertussis. This is supported by our finding published previously of paroxysmal cough in 55.2% of patients with cultures negative for *B pertussis*.[3]

On follow-up, typical symptoms of pertussis such as paroxysms and whooping were reported in 90.2% and 78.9% of patients, respectively. Interestingly, none of the the clinical findings varied by age. Recently, similar observations were made in the United States and Canada, although many of the cases occurred among vaccinated individuals.[9,12] Of cases reported to the CDC, 83% had paroxysms and 54% whooped.[9] In contrast with paroxysms and whooping, vomiting was reported less frequently in adolescents and adults. Halperin and associates[12] noted the occurrence of whooping less frequently in children >10 years, compared with those <10 years, whereas paroxysmal cough and vomiting showed no age dependency. In the report from the CDC, the rates of apnea and cyanosis decreased from 55% and 51% in infants <6 months of age to 12% and 29% in adults, respectively.[9] These rates appear to be unusually high and, therefore, it seems doubtful that what they reported really represents the impressive clinical symptoms of apnea and cyanosis. In our series, 15.9% of cases in infants <6 months of age, compared with only .1% of those in older patients, were complicated by apnea. In hospitalized children, the rates for apnea are biased,[18] because apnea may be life-threatening and, therefore, is considered to be an indication for intensive hospital care.

In only 62.1% of patients in our study was the total duration of cough >4 weeks. In 17.4%, it was even ≤3 weeks, thus not fulfilling the clinical part of the World Health Organization (WHO) definition for pertussis.[19] Similar observations were made by us and others before. In our previous report, 25.5% of culture-proven cases coughed for ≤3 weeks[3] and in the large US series, the rate was 24%.[9]

Unfortunately, because information on antibiotic use was only requested for the period before NPS collection, we cannot reliably assess the role of antibiotics on severity and frequency of symptoms in our patients. It is generally believed and supported by clinical observations that erythromycin is more effective against pertussis when given prophylactically or early (ie, within 7 days) after onset of symptoms than if given later during disease.[20–22] If given to patients in the paroxysmal stage of pertussis, erythromycin does not seem to reduce symptoms.[23] Our data appear to confirm these previous observations; in patients with early initiation of erythromycin treatment, a trend toward shorter and less severe illness was noted, compared with those with late erythromycin use.

The high rate of *B pertussis* infections of short duration has implications on calculated efficacy rates of pertussis vaccines in trials when the clinical case definition is based on the WHO definition; this requires ≥21 days of paroxysmal cough. For example, in a recent study in Italy, the efficacy rates for two different three-component acellular pertussis vaccines were 84% based on the WHO case definition, compared with 71% for any cough with a duration of ≥7 days.[24]

As part of this surveillance study, we had the opportunity to study WBC counts in a large number of unvaccinated, nonhospitalized patients with culture-confirmed *B pertussis* infections. Leukocytosis attributable to lymphocytosis was recognized as a hallmark of pertussis infection 100 years ago.[25] It is attributable to pertussis toxin, and it is the only known systemic manifestation of this toxin.[16] There are only a few detailed descriptions of leukocyte and/or lymphocyte values in patients with pertussis.

In a series of 199 children hospitalized for pertussis, Kaufman and Bruyn[26] noted that on admission, 57% had a WBC count of >20 000/mm.^{3} The WBC count was unrelated to age and did not correlate with the subsequent clinical course. In contrast, Lagergren[25] found marked differences in leukocyte and lymphocyte counts when comparing 39 hospitalized children <6 months of age, with 52 patients 6 months to 12 years of age during the first 2 weeks after admission. In the young age group, 33% and 36% had leukocyte counts ≥15 000/mm^3 and lymphocyte counts ≥11 000/mm,^{3} compared with 71% and 63% in the older age group, respectively. Both studies included cases diagnosed on clinical criteria only. More recently, Gordon and colleagues[18] found no such age differences in 173 laboratory-confirmed cases; of 108 children <6 months, 56% had leukocyte values ≥15 000/mm^3 and 56% had lymphocyte values of ≥10 000/mm.^{3} The respective figures for 65 children >6 months were 54% and 46%. It should be noted that none of these studies considered the age dependency of normal WBC counts. For example, the upper limit of the 95% CI for mean leukocyte blood counts is 17 500/mm^3 in children 6 to 12 months of age, compared with 14 500/mm^3 in children 4 to 6 years of age.[8]

Our approach was to use age-specific threshold values to establish the rates of abnormally high leukocyte and lymphocyte blood counts in patients with *B pertussis* infection. As expected, mean leukocyte

and lymphocyte values were higher in patients with confirmed pertussis, compared with controls. Overall, 72% and 76% of unvaccinated patients had leukocyte and lymphocyte values above the normal mean, and 30% and 35% of the values were above the upper limit of the 95% CI of the mean leukocyte and lymphocyte counts, respectively. These percentages were significantly higher than those for controls, in which only two (2%) children with abnormally high leukocyte counts and four (10%) children with abnormally high lymphocyte counts were identified.

We did not see a higher rate of abnormal values in children >6 months, compared with young infants, but rather observed similar rates in all age groups studied. This is in accordance with the results of Gordon et al,[18] as stated above. It is obvious from our data that leukocytosis and/or lymphocytosis are strong and specific indicators for *B pertussis* infection, but the sensitivity of this finding is limited.

CONCLUSION

In summary, the data presented allow an analysis of selected clinical findings of *B pertussis* infection in unvaccinated patients. With the exception of a higher rate of complications in infants compared with older children, the frequency of characteristic symptoms and high WBC counts was in general independent of the patients' age. Classical symptoms such as paroxysmal cough, posttussive vomiting, and whooping were observed in most patients affected. The majority of patients had lymphocytosis, but significantly elevated values were observed in only 35%. In spite of what appears to have been typical findings, the clinical diagnosis of pertussis was not made when the patient was evaluated initially in half of the patients. This suggests that quantitative aspects of illness (ie, number of paroxysms per day and their duration) are important, and they were not assessed in our study. The total duration of cough was ≤3 weeks in 17.4% of the patients, thus not fulfilling one requirement of the WHO's clinical case definition. Overall, severity of pertussis in this study was less than that observed in other large case series published previously.

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