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ORIGINAL ARTICLE

Clinical Characteristics of Hospitalized Infants With Laboratory-Confirmed Pertussis in Guatemala

Varun K. Phadke,[1] John P. McCracken,[2] Jennifer L. Kriss,[3] Maria R. Lopez,[2] Kim A. Lindblade,[4] Joe P. Bryan,[4,5] Miguel E. Garcia,[6] Carlos E. Funes,[7] and Saad B. Omer[3,8,9]

[1]Division of Infectious Diseases, School of Medicine, [3]Department of Epidemiology and [8]Hubert Department of Global Health, Rollins School of Public Health, and [9]Emory Vaccine Center, Emory University, Atlanta, Georgia; [2]Center for Health Studies, Universidad del Valle de Guatemala, Guatemala City; [4]Division of Global Health Protection, Centers for Disease Control and Prevention, Central American Regional Office, Guatemala City, Guatemala; [5]Division of Global Health Protection, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia; [6]Department of Pediatrics, Hospital Nacional de Cuilapa, Santa Rosa, Guatemala; and [7]Department of Pediatrics, Hospital Regional de Occidente, Quetzaltenango, Guatemala

Background. Pertussis is an important cause of hospitalization and death in infants too young to be vaccinated (aged <2 months). Limited data on infant pertussis have been reported from Central America. The aim of this study was to characterize acute respiratory illnesses (ARIs) attributable to *Bordetella pertussis* among infants enrolled in an ongoing surveillance study in Guatemala.

Methods. As part of a population-based surveillance study in Guatemala, infants aged <2 months who presented with ARI and required hospitalization were enrolled, and nasopharyngeal and oropharyngeal swab specimens were obtained. For this study, these specimens were tested for *B pertussis* using real-time polymerase chain reaction (PCR).

Results. Among 301 infants hospitalized with ARI, we found 11 with pertussis confirmed by PCR (pertussis-positive infants). Compared to pertussis-negative infants, pertussis-positive infants had a higher mean admission white blood cell count (20 900 vs 12 579 cells/μl, respectively; $P = .024$), absolute lymphocyte count (11 517 vs 5591 cells/μl, respectively; $P < .001$), rate of admission to the intensive care unit (64% vs 35%, respectively; $P = .054$), and case fatality rate (18% vs 3%, respectively; $P = .014$). Ten of the 11 pertussis-positive infants had cough at presentation; the majority (80%) of them had a cough duration of <7 days, and only 1 had a cough duration of >14 days. Fever (temperature ≥ 38°C) was documented in nearly half (45%) of the pertussis-positive infants (range, 38.0–38.4°C).

Conclusions. In this study of infants <2 months of age hospitalized with ARI in Guatemala, pertussis-positive infants had a high rate of intensive care unit admission and a higher case fatality rate than pertussis-negative infants.

Keywords. case definitions; Guatemala; infants; pertussis.

Pertussis remains a significant cause of morbidity and death in young children, particularly infants <2 months of age who are too young to be vaccinated [1–3]. Interventions to prevent pertussis in this age group—including the immunization of pregnant and postpartum women, close contacts of young infants, and health care workers—have been introduced in some countries [4–8]. Although maternal immunization with pertussis-containing vaccines is 1 of the most effective strategies, it is not routine in many developing countries. To support the introduction of routine maternal pertussis immunization in low- and low-to-middle-income countries, high-quality data on infant pertussis epidemiology are needed [9]. In Latin America, data from surveillance studies of infant pertussis in Mexico [10], Costa Rica [11], Panama [12], Argentina [13], and Brazil [14] have been reported; however, similar data from other countries in the region, including many in Central America, are lacking [15].

Many Latin American countries conduct pertussis surveillance using the World Health Organization (WHO) or US Council of State and Territorial Epidemiologists (CSTE) case definitions for pertussis [16, 17] (Table 1). However, during recent pertussis epidemics in the United States and the United Kingdom, observational studies found that the clinical presentation of laboratory-confirmed pertussis in young infants was often atypical when viewed in the context of these published case definitions [18–20]. Given these observations, a significant proportion of pertussis cases might be unrecognized and the burden underestimated in low- and low-to-middle-income countries.

To begin to address this issue, we used data from a surveillance study of acute respiratory illness (ARI) hospitalizations in Guatemala [21], where maternal pertussis vaccination is not routine, and we identified pertussis among hospitalized infants aged <2 months by testing nasopharyngeal (NP) and/or oropharyngeal (OP) specimens using a real-time polymerase chain reaction (rt-PCR) assay for *Bordetella pertussis*. Using data from parental interviews and medical charts, we characterized the

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Correspondence: V. K. Phadke, MD, 49 Jesse Hill Jr. Dr, Atlanta, GA 30303 (vphadke@emory.edu).

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Table 1. Selected Case Definitions for Pertussis

Definition Used and Year (Reference)	Age (y)	Clinical Criteria: Cough Duration (days)	Clinical Criteria: Associated Features	Laboratory Criteria (Tests for *B pertussis*)	Epidemiologic Criteria	Interpretation
WHO, 2003 [29]	Any	≥14	Paroxysmal cough, inspiratory whooping, or posttussive vomiting	Positive culture, positive PCR, or positive paired serology	None	Clinically confirmed: met clinical criteria only or physician diagnosis of pertussis Laboratory confirmed: met clinical and laboratory criteria
CSTE, 2014 [33]	>1	≥14	Paroxysmal cough, inspiratory whooping, or posttussive vomiting	Positive culture or positive PCR	Contact with a person with laboratory-confirmed pertussis	Probable: met clinical criteria; confirmed: met clinical criteria and had positive PCR, met clinical and epidemiologic criteria, or had positive culture with cough of any duration
	<1	Any	Paroxysmal cough, inspiratory whooping, posttussive vomiting, or apnea (with or without cyanosis)			Probable: same as for patients aged >1 y, met clinical criteria for those aged <1 y and positive PCR, or met clinical criteria for those aged <1 y and epidemiology criteria Confirmed: same as for age >1 y

Abbreviations: WHO, World Health Organization; CSTE, Council of State and Territorial Epidemiologists; PCR, polymerase chain reaction.

epidemiologic and clinical characteristics of pertussis in this vulnerable population.

METHODS

Surveillance and Case Ascertainment

As part of a collaboration between the Guatemalan Ministry of Health, the US Centers for Disease Control and Prevention (CDC), and the Universidad del Valle de Guatemala (UVG), surveillance of infants hospitalized with ARI is being conducted in 2 hospitals in Guatemala (Hospital Nacional de Cuilapa, Santa Rosa, and Hospital Regional de Occidente, Quetzaltenango). Full details of these surveillance sites were provided in a previous report [21]. ARI in children aged <2 years was defined as (1) at least 1 sign of acute infection (a temperature of ≥38°C or ≤35.5°C, an abnormal white blood cell [WBC] count [defined as <5550 or >11 000 cells/μl], or an abnormal differential) and (2) at least 1 respiratory sign/symptom (rapid breathing, cough, sputum production, pleuritic chest pain, hemoptysis, dyspnea, or sore throat [apnea was not included]) or inability to feed, noisy breathing, or nasal flaring. After February 2011, we also included children aged <5 years who satisfied the WHO Integrated Management of Childhood Illness (IMCI) clinical criteria for empiric therapy of suspected pneumonia (or severe pneumonia) in those aged 2 months to 5 years [22]. These criteria require any 1 of the following: cough with rapid breathing (≥50 breaths/minute for children aged 2–12 months and ≥40 breaths/minute for children aged 12 months to 5 years), chest in-drawing, stridor, or any general danger sign (defined as the inability to drink or breastfeed, persistent vomiting, loss of consciousness, lethargy, or convulsions [again, apnea was not included]) [22]. For this study, we focused on ARI hospitalizations in infants aged <2 months between 2009 and 2012.

Data Collection

Clinical and laboratory data of the enrolled infants were collected by surveillance nurses from parental interviews and medical charts. NP and OP swabs were collected in line with best practice guidance from the CDC. Study nurses donned masks, goggles, and gloves before NP/OP swab sampling, they opened the transport medium container only around the time of specimen collection, and swabs were collected from hospitalized infants in locations remote from those used for pertussis vaccine storage or preparation. After collection, NP/OP swabs were placed in viral transport medium (NP and OP swabs combined in 1 vial) and transported to the Universidad del Valle de Guatemala laboratory for rt-PCR testing.

For this study, these specimens were tested for *B pertussis* by an rt-PCR assay using reagents and protocols described by Tatti et al [23]. All rt-PCR assays on NP swab specimens were conducted alongside a *B pertussis*–positive and a *B pertussis*–negative control. During the extraction process, negative controls were included to ensure that no cross-contamination between samples occurred. Furthermore, an internal positive control (ribonuclease P [RNase P]) was used to verify NP sample quality (the cycle threshold [C_t] values for RNase P for all the specimens in this study were <40). Specimens that tested positive by PCR for both insertion sequence IS*481* (C_t < 40) and pertussis toxin subunit S1 (ptxS1) (C_t < 40) were considered positive for *B pertussis*. Specimens that tested positive only for IS*481* (C_t < 35) and negative for ptxS1 were considered positive for *Bordetella* species, and those with a C_t value for IS*481* that was ≥35 and <40 were considered indeterminate. Specimens that tested positive for only ptxS1 (C_t < 40) but tested negative for IS*481* were considered positive for *Bordetella parapertussis*. We did not perform additional PCR testing using *Bordetella holmesii*–specific targets.

Data Analysis

We conducted descriptive analyses of baseline characteristics, clinical features, and outcomes in relation to pertussis PCR test results. We used χ^2 and t tests to assess differences in proportions and means between the comparison groups. Differences

were considered statistically significant at a P value of <.05. SAS 9.3 (SAS Institute, Cary, NC) was used for all analyses.

Human Subjects

The protocol for the overall surveillance study was approved by the ethics review committees of the Universidad del Valle (Guatemala City, Guatemala), the US CDC (Atlanta, GA), and the Guatemala Ministry of Public Health and Social Welfare (Guatemala City, Guatemala). This study was exempted from additional review. Eligible infants who were hospitalized with ARI were enrolled after their parents or guardians provided written informed consent [21].

RESULTS

During the surveillance period, 355 infants aged <2 months were hospitalized with ARI in the study hospitals in Santa Rosa and Quetzaltenango. Of these infants, 323 (91%) were enrolled into the overall surveillance study, and an NP/OP swab specimen was obtained from 319 (90%) of them. A total of 301 aliquots (94% of the NP/OP specimens collected) were available for rt-PCR testing for *B pertussis*, and data from only these subjects were used in subsequent analyses. Of these 301 subjects, 186 (62%) were enrolled before February 2011 on the basis of the ARI case definition (although 160 of them also met the WHO IMCI clinical criteria). After February 2011, 22 (7%) subjects were enrolled on the basis of ARI definition alone, 23 (8%) were enrolled on the basis of WHO IMCI criteria alone, and 70 (23%) met both the ARI and WHO IMCI case definitions for enrollment. Of the 301 infants with an NP/OP swab specimen available for testing, 11 (3.7%) tested positive for *B pertussis* (hereafter referred to as pertussis-positive infants), and 1 (0.3%) tested positive for *B parapertussis*.

Baseline Characteristics

Seven (64%) of the 11 pertussis-positive infants were from the Santa Rosa site, and 4 (36%) were from the Quetzaltenango site. The mean age of the pertussis-positive infants was 36.8 days (standard deviation, 11 days; range 22–52 days). In this group, 7 (37%) infants were male, 10 (91%) were breastfed, and 3 (27%) had been born prematurely (reported as a dichotomous variable by the parents; specific gestational age data were not available for this analysis). No significant differences between pertussis-positive and pertussis-negative infants were found in the baseline characteristics (age, sex, department of residence, breastfeeding status, and preterm birth) (Table 2).

Table 2. Baseline Data for Infants Aged <2 Months Tested for Pertussis: Guatemala, 2007–2012

Characteristic	Pertussis-Positive Infants (n = 11)	Pertussis-Negative Infants (n = 290)	*P*
Age (mean [range]) (days)	36.8 (22–52)	33.8 (1–60)	NS
Male sex (n [%])	7 (63.6)	149 (51.4)	NS
Breastfed (n [%])	10 (90.9)	256 (88.6)	NS
Preterm birth (n [%])	3 (27.3)	82 (28.4)	NS
Residence (n [%])			
Santa Rosa	7 (63.6)	146 (50.3)	NS
Quetzaltenango	4 (36.4)	144 (49.7)	NS

Abbreviation: NS, nonsignificant ($P > .05$).

Outcomes and Clinical Features

The clinical course and outcomes of the 11 infants are shown in Table 3. Two (18%) deaths occurred among the 11 pertussis-positive infants, whereas 10 (3%) deaths occurred among the 290 pertussis-negative infants (P = .014). One of the pertussis-positive infants who died was born prematurely. A greater proportion of the pertussis-positive infants required admission to the intensive care unit (ICU) than the pertussis-negative infants (64% vs 35%), although this difference was not statistically significant (P = .054). Among infants admitted to the ICU, the pertussis-positive and pertussis-negative infants had similar mean lengths of stay (5.9 vs 5.3 days, respectively; P = .712). Three (27%) of the 11 pertussis-positive infants had been diagnosed with pertussis clinically by a treating physician, compared to 4 (1%) of the 290 pertussis-negative infants (P < .001).

Five (45%) of the 11 pertussis-positive infants had a fever (temperature ≥ 38°C) within the first 24 hours of hospitalization, with temperatures ranging from 38.0 to 38.4°C, but this was not significantly different from the proportion (178 [61%]) of the 290 pertussis-negative infants who had fever. Seven (64%) of the 11 pertussis-positive infants met clinical criteria for empiric treatment for presumed pneumonia, defined according to the WHO IMCI handbook criteria for children aged 2 months to 5 years [22], compared to 252 (87%) of the 290 pertussis-negative infants (P = .024). The proportion of the 11 pertussis-positive infants who had seizures was higher than that of the 290 pertussis-negative infants (18% vs 5%, respectively) (further clinical details on the seizures were not captured), but this difference was not statistically significant (P = .067).

Hematologic parameters were available from 10 (91%) of the 11 pertussis-positive infants and 218 (75%) of the 290 pertussis-negative infants. The mean admission WBC count among the 11 pertussis-positive infants (20 900 cells/μl; range, 8900–36 100) was greater than that for the 290 pertussis-negative infants (12 579 cells/μl, range 3000–71 900) (P = .024). The mean admission absolute lymphocyte count (ALC) was similarly significantly higher in the 11 pertussis-positive infants (11 517 cells/μl; range, 3391–18 880) than in the 290 pertussis-negative infants (5591 cells/μl; range, 132–22 792) (P < .001). The mean admission WBC count and ALC were not significantly higher in the pertussis-positive infants who died than in those who survived.

Table 3. Outcomes and Clinical Characteristics of Infants Aged <2 Months Tested for Pertussis: Guatemala, 2007–2012

Characteristic	Pertussis-Positive Infants (n = 11)	Pertussis-Negative Infants (n = 290)	*P*
Outcomes			
Death (n [%])	2 (18.2)	10 (3.4)	.014
ICU admission (n [%])	7 (63.6)	102 (35.2)	NS
ICU length of stay (mean [range]) (days)	5.9 (2–15)	5.3 (1–24)	NS
Clinical characteristics			
Cough (n [%])	10 (91)	253 (87)	NS
Cough duration before admission (mean [range]) (days)	5.3 (1–15)	4.3 (1–30)	NS
Paroxysmal cough (n [%])[a]	0 (0)	14 (4.8)	NS
Whoop (n [%])[a]	1 (9.1)	12 (4.1)	NS
Posttussive emesis (n [%])[a]	0 (0)	9 (3.1)	NS
Fever (temperature ≥ 38°C) (n [%])	5 (45.5)	178 (61.4)	NS
Cyanosis (n [%])	1 (9.1)	5 (1.7)	NS
Pneumonia (n [%])[b]	7 (63.6)	252 (86.9)	.029
Seizure (n [%])	2 (18.2)	15 (5.2)	NS
Laboratory characteristics			
Admission WBC count (mean [range]) (per μl)	20 900 (8900–36 100)	12 579 (3000–71 900)	.024
Admission ALC (mean [range]) (per μl)	11 517 (3391–18 880)	5591 (132–22 792)	<.001
Diagnosed with pertussis by a physician (n [%])	3 (27.3)	4 (1.4)	<.001

Abbreviations: ALC, absolute lymphocyte count; ICU, intensive care unit; NS, nonsignificant (*P* > .05); WBC, white blood cell.

[a]Data collected only when cough duration exceeded 7 days.

[b]Presumed pneumonia, defined according to the Integrated Management of Childhood Illness clinical criteria.

Detailed clinical information for the 11 pertussis-positive infants collected at the time of presentation is summarized in Table 4. In terms of presenting symptoms, 10 (91%) of the 11 pertussis-positive infants had a cough at the time of presentation, and their mean cough duration before admission (defined as the duration of cough before hospitalization) was 5.3 days (standard deviation, 4.3 days; range, 1–15 days). The cough durations before hospitalization did not differ between the pertussis-positive and pertussis-negative infants ($P = .354$). Of the 10 pertussis-positive infants who had a cough at the time of hospitalization, 8 (80%) had been coughing for <7 days, and of the remaining 2 infants, only 1 had been coughing for longer than 14 days. In the main surveillance study, more specific details about the nature of the cough illness, including the presence of paroxysmal cough, whoop, or posttussive emesis, were not collected from infants who had been coughing for ≤7 days at the time of hospitalization. However, in the 2 pertussis-positive infants who had been coughing for >7 days, only 1 had whoop, and neither infant had had paroxysmal cough or posttussive emesis. In terms of laboratory findings, hematologic data from 10 of the 11 pertussis-positive infants were available, and of these infants, 5 (50%) had an admission WBC count greater than 20 000 cells/μl, and 7 (70%) had an admission ALC greater than 10 000 cells/μl.

Each infant had previously undergone testing for respiratory syncytial virus (RSV) and influenza A and B as part of the overall ARI surveillance study; among the 11 pertussis-positive infants, 2 (18%) were coinfected with RSV and none had concomitant influenza. Three (33%) of 9 pertussis-positive infants for whom interpretation of chest radiography (CXR) was available had findings of alveolar consolidation, although in 1 patient, CXR was not performed until hospital day 9. Two (22%) additional pertussis-positive infants had infiltrates without definite consolidation, as defined by the WHO radiological criteria for pneumonia [24].

DISCUSSION

To our knowledge, this is the first report of the epidemiologic and clinical characteristics of laboratory-confirmed pertussis in infants from Guatemala. Using rt-PCR, we identified 11 infants with laboratory-confirmed pertussis among a group of 301 infants aged <2 months hospitalized with ARI in 2 study hospitals in Guatemala. A high proportion of these pertussis-positive infants had severe disease with complications, including 7 (64%) who required ICU admission and 2 (18%) who died. These rates of complications are similar to those reported for hospitalized infants with pertussis from a variety of geographic regions [11, 19, 20, 25–28], including several countries in Latin America, such as Mexico [10], Costa Rica [11], Panama [12], Argentina [13], and Brazil [14]. It is notable that in recent years, these same countries have experienced a resurgence of pertussis, with a number of infant hospitalizations and deaths, and have since introduced routine maternal pertussis immunization into their national vaccination programs [17].

On basis of our clinical data, only 1 of the pertussis-positive infants met the clinical criteria specified by the WHO case definition for pertussis, which requires a cough duration of ≥14 days at the time of presentation [29]. However, 2 other pertussis-positive infants who did not meet the WHO clinical criteria were diagnosed with pertussis by a physician. In our study, the majority (80%) of pertussis-positive infants actually had a cough duration of ≤7 days at the time of hospitalization. This finding is similar to that reported for infant pertussis by investigators in other countries [12, 18–20, 27, 28, 30]. Infants with pertussis can also present with other atypical manifestations (ie, not captured by the WHO case definition for pertussis), such as apnea and seizures [31]; seizures were associated with death in 1 recent series [32]. We did not have data on apnea, but 18% of the pertussis-positive infants in our series had seizures. Together, these data suggest that pertussis might be an important underrecognized cause of severe respiratory disease in young infants and should not be excluded from the differential diagnosis on the basis of the absence of classic clinical features. Furthermore, infant pertussis is likely to be

Table 4. Clinical Characteristics of Hospitalized Infants Aged <2 Months With Laboratory-Confirmed Pertussis

Patient No.	Age (days)	Sex	Duration of Cough (days)	Temperature (°C)[a]	Paroxysmal Cough[b]	Whoop[b]	Posttussive Emesis[b]	Cyanosis	Pneumonia[c]	CXR Findings	Seizure	Coinfection (RSV, Influenza A or B)	WBC Count (cells/μl)	ALC (cells/μl)	Outcome
1	22	M	None	37.0	NA	NA	NA	N	Y	No infiltrate	N	N	21 800	10 377	Survived
2	23	F	1	38.0	NA	NA	NA	N	N	No infiltrate	N	N	23 000	14 260	Died
3	26	M	7	36.5	NA	NA	NA	N	Y	Other infiltrate[e]	Y	N	8900	3391	Survived
4	30	F	3	38.4	NA	NA	NA	N	Y	Consolidation[d]	N	N	36 100	18 880	Survived
5	34	M	15	38.0	N	N	N	N	Y	Other infiltrate[e]	N	Y (RSV)	10 400	6552	Survived
6	35	M	1	37.0	NA	NA	NA	N	N	No CXR	N	N	NA	NA	Survived
7	40	M	5	37.0	NA	NA	NA	Y	N	Not interpreted	Y	N	18 000	10 422	Died
8	45	F	6	37.0	NA	NA	NA	N	N	Consolidation	N	N	26 200	15 222	Survived
9	46	M	3	37.0	NA	NA	NA	N	Y	No infiltrate[e]	N	N	19 800	14 098	Survived
10	52	M	9	38.0	N	Y	N	N	Y	Consolidation	N	Y (RSV)	33 100	17 675	Survived
11	52	F	3	38.0	NA	NA	NA	N	Y	No infiltrate	N	N	11 700	4294	Survived

Abbreviations: ALC, absolute lymphocyte count; CXR, chest radiography; F, female; M, male; N, no; NA, not available; RSV, respiratory syncytial virus; WBC, white blood cell; Y, yes.

[a]Highest temperature within the first 24 hours of medical care.

[b]Only those with a cough duration exceeding 7 days were asked about paroxysmal cough, whoop, or posttussive emesis.

[c]Presumed pneumonia, defined according to the Integrated Management of Childhood Illness clinical criteria for children aged 2 months to 5 years.

[d]Chest radiography was performed on hospital day 9.

[e]Infiltrate was interpreted by a hospital radiologist and 2 clinicians but not by a study radiologist.

substantially underreported in countries that conduct surveillance using the WHO clinical criteria.

To begin to address this problem in the United States, the CSTE updated its pertussis surveillance case definition in 2014 to better capture disease in infants <1 year of age. The updated CSTE definition no longer requires a minimum duration of cough for reporting probable cases of pertussis in this age group, and apnea was also added to the list of associated clinical features that would satisfy the revised case definition in young infants [33]. Because we did not have data on the typical associated features of pertussis (paroxysmal cough, whoop, or posttussive emesis) for the pertussis-positive infants with a cough duration of <7 days, or data on apnea for any of the infants in the study, we could not assess the performance of the new CSTE case definition in our sample. It is important to note that the CSTE definition requires laboratory confirmation of pertussis with culture for infants <1 year of age to be classified as confirmed as a case. Therefore, according to CSTE criteria, even infants hospitalized with severe pertussis whose disease is confirmed with PCR but who did not have a cough for ≥14 days would be classified only as having a probable case.

Another notable finding from our study is that nearly half (45%) of the pertussis-positive infants had a documented fever within the first 24 hours of hospitalization. It is possible that fever in the pertussis-positive infants in our study was attributable to concomitant or secondary bacterial or viral infection; for example, 3 of the 5 infants with fever had radiographic infiltrates (2 met the WHO radiological criteria for pneumonia), and evidence of RSV infection was found in 2 infants by PCR testing. We did not have additional data on the course of fever to speculate on the potential etiologies of fever in these infants. However, the contribution of pertussis infection to their clinical presentation and the course of their illness should not be overlooked. Although fever is generally thought to be an uncommon manifestation of pertussis in this age group, especially compared to common viral pathogens, there is considerable variability in the prevalence of fever that has been reported in descriptive studies of infant pertussis. For example, in 2 recent community-based surveillance studies of infant pertussis in Pakistan and Zambia, no infants with PCR-confirmed pertussis had fever [34, 35]. In contrast, in other analyses of hospitalized infants who were found to have laboratory-confirmed pertussis, the prevalence of fever was much higher; in 1 such study in South Africa, the prevalence was nearly 25% [36], and in a study of pertussis-positive infants admitted to pediatric ICUs in the United Kingdom, 44% of the infants had fever [19]. Last, in a secondary analysis of data from a randomized controlled trial of maternal influenza immunization in South Africa, for which the surveillance definition for respiratory illness required the presence of fever, nearly one-fourth (24.3%) of the infants with laboratory-confirmed pertussis had fever [37]. It is notable that in 2011, the Global Pertussis Initiative proposed age-stratified clinical case definitions to account for the unique features of pertussis in younger children and stipulated the presence of "cough and coryza with no or minimal fever" in children aged 0 to 3 months [38]. Although this definition improves on the WHO clinical criteria for pertussis (which did not account for age), systematically excluding infants with fever from confirmatory laboratory testing for *B pertussis* infection can lead to an underestimation of the pertussis burden in young infants, including the important burden of pertussis coinfection with other respiratory pathogens and the burden of pertussis in critically ill infants. Indeed, 1 recent study specifically identified fever as a predictor of more severe pertussis in children [39].

There are several limitations to our study. Because our sample was limited to hospitalized infants, who therefore met the definition for a severe case, we cannot comment on the clinical characteristics of less severe pertussis in nonhospitalized infants in this population or on the background incidence of pertussis in Guatemala during the surveillance period. As a result, it is difficult to assess the potential impact of various control strategies, including routine maternal pertussis immunization, in our population. Similarly, our ARI case definition, which required either fever or an abnormal white blood cell count, also might have created a bias toward the most severe pertussis cases. Because we obtained NP/OP swab specimens from only 90% of eligible infants (or 99% of enrolled infants), and of these infants, only 93% were available for this analysis, it is possible that selection bias was introduced, because the infants who did not undergo testing might have been systematically different from those who did. However, we note that this rate of testing (93% of enrolled infants) is similar to that of enrolled subjects for whom laboratory data were available in previously published analyses of other respiratory pathogens in this surveillance cohort (eg, RSV [40] and human metapneumovirus [41]). The small number of cases in our study and the lack of data on the symptoms of early (ie, coryza) or typical (ie, paroxysmal cough, whoop, and posttussive emesis) pertussis also limited our ability to identify characteristics that might be predictive of pertussis as a cause of ARI. Also, because apnea was not part of the clinical criteria used for enrollment, and this symptom is now recognized as a common manifestation of pertussis in young infants [31], we might have missed infants with pertussis who might have differed from the infants included in our analysis. Ultimately, improved characterization of severe infant pertussis in diverse settings is essential for guiding efforts to decrease morbidity and death in this vulnerable age group.

Some of the observed differences in the hospital courses and clinical outcomes between the pertussis-positive and pertussis-negative infants might have been a result of unmeasured differences in their prehospital course; for example, the infants who tested positive for pertussis might have presented later in the course of their ARI than did pertussis-negative infants, as evidenced by the longer duration of fever before presentation, which could partly explain the observed differences in clinical severity (eg, higher case-fatality rate). However, other than fever duration, there were no significant differences in the types of symptoms at the time of presentation between pertussis-positive and pertussis-negative infants, which indicates that the differences in clinical outcomes were likely attributable to pertussis itself. Similarly, it is possible that some of the pertussis-positive infants in our study had an alternative diagnosis underlying their clinical presentation and that *B pertussis* was identified incidentally. However, the 11 pertussis-positive infants differed from the 290 pertussis-negative infants in several important parameters, including admission WBC count, admission ALC, proportion who required ICU admission, and case-fatality rate, which is consistent with other reports of infants hospitalized with pertussis monoinfection [18, 42]. A systematic difference in these parameters between the pertussis-positive and pertussis-negative infants would not be expected if the assay simply identified asymptomatic carriage of the organism.

CONCLUSIONS

In this sample of infants hospitalized with ARI in Guatemala, we found that pertussis-positive infants had a higher rate of complications and a higher mortality rate than pertussis-negative infants. Furthermore, most of the pertussis-positive infants would not have been captured by the existing WHO clinical case definition, which suggests that the burden of pertussis in young infants is likely to be underestimated in developing countries such as Guatemala. Improvements in current case definitions would enhance pertussis surveillance and guide implementation of strategies to prevent severe disease in young infants.

Notes

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