Does This Coughing Adolescent or Adult Patient Have Pertussis?

Paul B. Cornia, MD

Adam L. Hersh, MD

Benjamin A. Lipsky, MD

Thomas B. Newman, MD, MPH

Ralph Gonzales, MD, MSPH
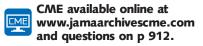
CLINICAL SCENARIO

A 73-year-old man presents to the clinic with a 3-week history of paroxysmal cough. He denies fever, chills, headache, myalgias, rhinorrhea, sore throat, hemoptysis, chest pain, dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. He has no inspiratory whoop but acknowledges 2 episodes of posttussive emesis. Physical examination findings of his heart and lungs are normal, as is a plain chest radiograph result. How much do the clinical findings change the likelihood that he has pertussis?

WHY IS THE CLINICAL EXAMINATION IMPORTANT?

Childhood vaccination for *Bordetella pertussis* (the cause of whooping cough) confers limited immunity that wanes after 5 to 10 years and rarely lasts more than 12 years.[1,2] Physicians often forget that a prolonged cough in an adult or adolescent may be due to pertussis.[3,4] The severe cough of pertussis can cause subconjunctival hemorrhage, rib

See also Patient Page.

CME **CME available online at www.jamaarchivescme.com and questions on p 912.**

Context Pertussis is often overlooked as a cause of chronic cough, especially in adolescents and adults. Several symptoms are classically thought to be suggestive of pertussis, but the diagnostic value of each of them is uncertain.

Objective To systematically review the evidence regarding the diagnostic value of 3 classically described symptoms of pertussis: paroxysmal cough, posttussive emesis, and inspiratory whoop.

Data Sources, Study Selection, and Data Extraction We searched MEDLINE (January 1966–April 2010), EMBASE (January 1969 to April 2010), and the bibliographies of pertinent articles to identify relevant English-language studies. Articles were selected that included children older than 5 years, adolescents, or adults and confirmed the diagnosis of pertussis among patients with cough illness (of any duration) with an a priori–defined accepted reference standard. Two authors independently extracted data from articles that met selection criteria and resolved any discrepancies by consensus.

Data Synthesis Five prospective studies met inclusion criteria; 3 were used in the analysis. Presence of posttussive emesis (summary likelihood ratio [LR], 1.8; 95% confidence interval [CI], 1.4-2.2) or inspiratory whoop (summary LR, 1.9; 95% CI, 1.4-2.6) increases the likelihood of pertussis. Absence of paroxysmal cough (summary LR, 0.52; 95% CI, 0.27-1.0) or posttussive emesis (summary LR, 0.58; 95% CI, 0.44-0.77) reduced the likelihood. Absence of inspiratory whoop was less useful (summary LR, 0.78; 95% CI, 0.66-0.93). No studies evaluated combinations of findings.

Conclusions In a nonoutbreak setting, data to determine the diagnostic usefulness of symptoms classically associated with pertussis are limited and of relatively weak quality. The presence or absence of posttussive emesis or inspiratory whoop modestly change the likelihood of pertussis; therefore, clinicians must use their overall clinical impression to decide about additional testing or empirical treatment.

JAMA. 2010;304(8):890-896   www.jama.com

fractures, urinary incontinence, hernias, posttussive syncope, or even intracranial hemorrhage and stroke from vertebral artery dissection.[5] Less dramatically, the cough keeps patients from sleeping, isolates them, and may cause concern about a serious undiagnosed condition.[5] Undiagnosed infected adolescents and adults may spread the illness to inadequately immunized children, in whom infection is more severe and potentially fatal.

Author Affiliations: Primary and Specialty Medical Care Service, Veterans Affairs Puget Sound Health Care System, and Department of Medicine, University of Washington School of Medicine, Seattle (Drs Cornia and Lipsky); Divisions of Pediatric Infectious Diseases (Dr Hersh) and General Pediatrics (Drs Hersh and Newman), Clinical Epidemiology (Drs Newman and Gonzales), and General Internal Medicine (Dr Gonzales), University of California, San Francisco.
Corresponding Author: Ralph Gonzales, MD, MSPH, Department of Medicine, University of California, San Francisco, 3333 California St, Box 1211, Ste 430, San Francisco, CA 94118 (ralphg@medicine.ucsf.edu).
The Rational Clinical Examination Section Editors: David L. Simel, MD, MHS, Durham Veterans Affairs Medical Center and Duke University Medical Center, Durham, NC; Drummond Rennie, MD, Deputy Editor.

Approach to Patients With Cough

Patients with persistent cough often contact their physician for advice.[6] Determining the duration of cough is a useful first step in narrowing the differential diagnosis of possible causes.[7] Recently developed guidelines classify cough as acute (<3 weeks), subacute (3-8 weeks), or chronic (>8 weeks).[8] Acute cough may be caused by a serious condition (eg, pneumonia, congestive heart failure, lung cancer, or pulmonary embolism), but the most common cause is a self-limited, viral upper respiratory tract infection (eg, the common cold). Subacute cough often represents persistence of an acute respiratory infection, eg, a viral or bacterial upper airway infection or a lower respiratory tract infection, and may spontaneously resolve.[9] If a respiratory infection did not precede the cough, clinicians should proceed with an evaluation for chronic cough.[8]

For persons who smoke or take angiotensin-converting enzyme inhibitors, the first step is to stop them. If the cough persists, it is most commonly caused by gastroesophageal reflux disease, asthma, or postnasal drip/chronic sinusitis (also known as upper airway cough syndrome).[10] Another recently identified common cause of chronic cough is nonasthmatic eosinophilic bronchitis, defined by cough accompanied by sputum showing eosinophils and without dyspnea, wheezing, airflow obstruction by spirometry, or airway hyperreactivity by methacholine provocation testing.[11,12] In addition to these well-recognized causes of persistent cough, physicians should be aware that pertussis also causes subacute and chronic cough.

Classic Stages of Pertussis Infection

Infection with *B pertussis* in a person without immunity is characterized by 3 phases: catarrhal, paroxysmal, and convalescent. The catarrhal phase usually lasts 1 to 2 weeks, but diagnosis during this stage is difficult. Symptoms are nonspecific and overlap with more common viral upper respiratory tract infections; eg, generalized malaise, rhinorrhea, and mild cough. Patients may have low-grade temperature elevations, but significant fever is atypical.[13] Two early findings that may be clinically useful are excessive lacrimation and conjunctival injection. An important piece of historical information for a patient presenting with a cough illness is whether the patient had recent sick contacts. The incubation period for *B pertussis* is relatively long (7-10 days) compared with most viral upper respiratory tract infections (1-3 days). Although by no means diagnostic, exposure to a person with a cough illness 1 to 2 weeks prior to the development of symptoms is more suggestive of pertussis, particularly if that contact belongs to a high-risk group for pertussis (eg, works with young children or lives in a community with low vaccination rates).

The paroxysmal stage begins during the second week of illness, with the hallmark symptom of coughing spells. A paroxysm is a series of coughs during a single expiration; these episodes often occur in groups throughout the day and night, with patients experiencing few symptoms between paroxysms.[13] A cough paroxysm causes low lung volumes, leading to a vigorous inspiration that may result in a whoop, particularly in infants and children, in whom the caliber of the trachea is smaller. Once seen or heard, this dramatic presentation is not soon forgotten. (See http://www.immunizationed.org/ for audio and video of examples of infants and children with pertussis infection.) Other classic symptoms that have been described at this stage are posttussive emesis or syncope. After about 2 to 3 months, the paroxysmal phase is followed by a gradual transition to the convalescent phase, characterized by a persistent but decreased frequency and severity of cough. Thus, the Chinese name for the pertussis illness, "the 100-day cough," is apt.

Symptoms of pertussis infection in previously immunized or infected adolescents and adults, in contrast with the classic symptoms observed in unimmunized infants and children, are variable and often atypical.[4,14] The predominant symptom may simply be a persistent cough. However, clinicians frequently do not consider pertussis infection in such cases.[3,4] Because of the relatively long incubation period, frequent nonspecific symptoms that overlap with other more common respiratory illnesses (eg, viral upper respiratory tract infections), and the difficulty culturing the organism combined with a lack of an alternative widely available and accepted diagnostic test, the true prevalence of pertussis infection is difficult to determine and subject to debate.[15]

Several recent studies have shown that pertussis is the cause of 12% to 32% of prolonged cough illnesses in adolescents and adults; for most patients, the duration of the cough illness is more than 3 weeks.[14] This range of prevalence represents a reasonable pretest probability estimate for pertussis as the cause of prolonged cough illness. It is unknown how frequently the classically described features of pertussis infection (ie, paroxysmal cough, inspiratory whoop, and posttussive emesis or syncope) occur among adolescents and adults.

Epidemiology of Pertussis Infection

Pertussis was a devastating illness with relatively high mortality rates in infants until a whole-cell vaccine was introduced in the United States in the late 1940s. Widespread pertussis vaccination of children led to a dramatic decline in disease incidence, from a peak of more than 250 000 reported cases in 1934 to a nadir of 1010 cases in 1976.[16] The incidence of the disease began to steadily increase in the early 1980s, however, with 11 647 cases reported in 2003.[17] Increasing clinician awareness and reporting of the disease with the use of more sensitive diagnostic techniques (especially polymerase chain reaction [PCR] testing) may be at least partly responsible for the increase in reported cases. The incidence of pertussis cases decreased in 2006,[18] perhaps suggesting that the cyclic epidemic peaks and valleys that occurred approximately every 2 to 5 years in the

prevaccine era are now recurring. The recent decreased incidence is unlikely to be attributable to use of the newly available acellular booster pertussis vaccine (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed [Tdap]) because the Advisory Council on Immunization Practices recommendations for booster vaccinations of adolescents[19] and adults[20] were not issued until 2006.

A substantial portion of the increasing incidence in reported pertussis cases over the past 3 decades is attributable to increased rates of the disease in adolescents and adults.[17,21] In the prevaccine era, more than 90% of reported cases of pertussis occurred in children younger than 10 years old.[21] Currently, about half of reported cases occur in adolescents and adults—persons aged 10 to 19 years account for 33% of infections; persons aged 20 years or older account for 23%.[16] Importantly, adolescents and adults with unrecognized pertussis are a reservoir of infection for infants and children. Infants, especially those younger than 6 months, and young children who have not been fully immunized are at the highest risk of hospitalization and pertussis-related morbidity and mortality. In epidemiologic studies, most infants acquire the infection from adolescents and adults in the household.[22] Among infants, increases occurred in both the incidence of reported cases[23] and of deaths[24] caused by pertussis between 1980 and 1999.

Laboratory Diagnosis of Pertussis

Bordetella pertussis is a gram-negative coccobacillus readily transmitted via respiratory secretions. Laboratory diagnostic tests for *B pertussis* infection include culturing a properly obtained nasopharyngeal specimen, performing direct fluorescent antibody staining or a PCR test, and testing for serum antibodies by enzyme-linked immunosorbent assays or Western blot.[25,26] The Centers for Disease Control and Prevention (CDC) endorses only the culture and PCR methods for diagnosis in community practice settings.[20] Specimens must be collected

from the ciliated respiratory epithelium of the posterior nasopharynx where *B pertussis* preferentially resides, not the anterior nares or throat.[27] It is best to obtain the specimen using a Dacron rather than a cotton swab, as the latter is toxic to *B pertussis* organisms. Calcium alginate swabs may also be used, but they interfere with the PCR assay. Nasopharyngeal secretions may also be obtained by intranares aspiration,[28] but few clinicians (especially nonpediatricians) have the necessary supplies at hand. Importantly, the sensitivities of PCR, serologic testing, and, particularly, culture decrease with the duration of illness. Thus, in adolescents and adults, who generally present to medical care only after several weeks of coughing, the sensitivity of the available diagnostic tests is likely to be reduced.

Because of its high specificity, culture of the organism from nasopharyngeal secretions is the criterion standard for diagnosis. However, the sensitivity of culture in clinical practice is only 30% to 60%[29] because of the fastidious nature of the *B pertussis* organism and the often prolonged duration of illness at the time of specimen collection. Other factors that may cause false-negative cultures include prolonged transport time of the specimen to the laboratory, delayed plating of the specimen after it arrives in the laboratory, and recent antibiotic treatment.[13] Growth of *B pertussis* requires special culture media and typically takes 7 to 10 days.

There are several methods for rapidly detecting pertussis antigens. Direct fluorescent antibody testing is inexpensive and provides rapid results but is no longer recommended because of its poor sensitivity and specificity. Polymerase chain reaction testing is being used more frequently because it offers increased sensitivity and specificity, detects even small numbers of organisms, is unaffected by recent use of antibiotics, and typically provides results within 1 to 2 days. However, PCR remains relatively costly, is not available in many settings, and can produce false-positive results.[30] Currently,

there is no US Food and Drug Administration (FDA)–approved PCR kit for pertussis, nor is there a standardized protocol for its use.

Serologic testing usually involves comparing the levels of pertussis antibodies in acute and convalescent (>4 weeks after the acute sample is obtained) serum samples; a substantial change in the titers (typically a 2- or 4-fold increase) suggests infection. Alternatively, a single sample with a level above a designated threshold or a substantial decrease in titer is sometimes considered diagnostic. Serologic testing is frequently used for epidemiologic or research purposes, but it is neither widely available nor standardized and no FDA-approved test exists.

Treatment of Pertussis

The CDC recommends that the thresholds for initiating testing and treatment be the same because of the contagiousness and public health implications of pertussis.[31,32] Antibiotic treatment during the catarrhal phase may decrease the duration and severity of cough, but the diagnosis is rarely considered during this early phase in adolescents and adults. Administering antibiotics later in the course of disease probably does not affect the course of symptoms but is recommended to help reduce spread of the infection. Persons with pertussis may remain contagious for a month or longer; most will eventually recover without antibiotic therapy.[13,32] The recommended antibiotic regimens are identical for treatment and postexposure prophylaxis (for close contacts of persons diagnosed as having pertussis).[32] Macrolide agents are preferred and typically eradicate *B pertussis* within 5 days.[13] Erythromycin has been the antibiotic of choice for decades; while it is inexpensive, the relatively frequent dosing (4 times daily) and high rate of adverse effects (most notably gastrointestinal distress) limit patient adherence. Available data suggest that azithromycin and clarithromycin, while more expensive, have comparable efficacy with and are bet-

ter tolerated than erythromycin, and these agents are increasingly used.[33-36] Trimethoprim-sulfamethoxazole is an alternative treatment for persons who are unable to tolerate macrolides.

Case Definition of Pertussis Infection

The CDC clinical case definition for endemic or sporadic cases of pertussis is a cough illness lasting 2 weeks or longer without other apparent cause with 1 or more of the following: paroxysms of coughing, inspiratory whoop, or posttussive vomiting.[37] We sought to estimate the accuracy of the classic symptoms for diagnosing pertussis infection in adolescents and adults in nonoutbreak settings.

METHODS

Literature Search Strategy

We searched MEDLINE (January 1966–April 2010; English-language articles only) using 3 strategies: (1) key words *pertussis* AND *cough* AND *duration*; (2) Medical Subject Heading (MeSH) term *whooping cough/epidemiology*; and (3) MeSH term *whooping cough/diagnosis* and EMBASE (January 1969–April 2010) using the search strategy *specificity* AND (*pertussis*/exp or *pertussis*), limited to human studies. Additional articles were identified from searching the bibliographies of retrieved articles. We reviewed the titles and abstracts of the identified articles for relevance and selected only articles that included children older than 5 years (expected to have completed primary vaccination), adolescents, or adult patients and that confirmed the diagnosis of pertussis among patients with cough illness (of any duration) with an accepted reference standard that we defined a priori (ie, culture, PCR, serologic testing, or clinical diagnosis based on definite clinical exposure).

Study Selection and Data Analysis

We excluded studies of outbreaks or active surveillance. Although the disease itself should not be different in an outbreak compared with patients that a typical clinician encounters in usual clinical practice, the threshold for seeking treatment and the reported clinical characteristics may be different because of spectrum bias.[38] Recent reports suggest that many patients initially presumed to have pertussis in outbreaks are actually false-positive cases,[39] raising further questions about the validity of clinical characteristics derived from these studies. The laboratory tests for the diagnosis of pertussis that we accepted as reference standards were culture, PCR, and pertussis toxin serologic testing (see "Laboratory Diagnosis of Pertussis" section above). We excluded studies that used only culture for laboratory diagnosis because of its low sensitivity. Although serologic testing is not currently recommended for clinical use, it is an important tool for research purposes. Serum antibodies to a variety of pertussis antigens, including pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae 2 and 3, or preparations of the whole organism may be measured. Because sensitivity and specificity are best for measurement of anti–pertussis toxin antibodies,[13] we included only studies that serologically diagnosed pertussis using this method.

We calculated sensitivity, specificity, summary likelihood ratios (LRs), and tests of heterogeneity for the classic symptoms of pertussis (paroxysmal cough, posttussive emesis, posttussive syncope, and inspiratory whoop). Because random-effects bivariate summary measures would not converge on a solution,[40] we used random-effects univariate summary measures. Data analyses were performed using Comprehensive Meta-analysis, version 2 (Biostat Inc, Englewood, New Jersey). For LR heterogeneity, we used the I^2 statistic, for which threshold values are qualitatively described as follows: less than 25% suggests homogeneity; 25% to 50%, low heterogeneity; 51% to 74%, moderate heterogeneity; and 75% or more, high heterogeneity.[41]

RESULTS

Study Characteristics

The MEDLINE literature search (eFigure; available at http://www.jama.com) yielded 2124 unique citations, of which we selected 52 for full-text review; from these articles, 5 met our prespecified inclusion criteria. The EMBASE literature search yielded 416 citations; 19 were selected for full-text review, but none met our inclusion criteria. Two of the 5 articles meeting inclusion criteria were subsequently excluded because of methodological limitations (eAppendix), leaving 3 articles[42-44] for data extraction. Most studies were excluded because they were conducted in an outbreak setting, did not use one of the diagnostic tests that we specified a priori, or did not contain extractable data. The number of participants in the included studies were large (n=102-212), which yielded reasonably narrow 95% confidence intervals (CIs) for the LRs; all studies were conducted in outpatient settings (TABLE 1). Two studies included primarily adults with some adolescents,[43,44] while 1 study included only children and adolescents.[42]

The studies were carried out in 3 different countries: South Korea, United Kingdom, and United States. Vaccination coverage for children in the United States[45] and the United Kingdom[46] are high; vaccine coverage information for South Korea is not available.

Duration of Cough

Using current guidelines for classifying cough,[8] 1 study had a median cough duration that fulfilled criteria for acute cough at presentation,[43] and 2 had median durations of subacute cough.[42,44] However, the total range for cough duration included patients across the span from acute to chronic.

Accuracy of Classic Symptoms in Diagnosis of Pertussis

All 3 studies included data on paroxysmal cough, posttussive emesis, and inspiratory whoop; none reported on posttussive syncope (TABLE 2). Among adolescent and adult patients with pertussis, paroxysmal cough is common, but the specificity of this finding is low. Posttussive emesis and whoop are less common, but both show greater specificity for pertussis infection.

In the pooled analyses, the positive LRs for the presence of posttussive emesis (LR, 1.8; 95% CI, 1.4-2.2) and inspiratory whoop (LR, 1.9; 95% CI, 1.4-2.6) are similar (Table 2). While statistically significant, the positive LR for paroxysmal cough is only slightly greater than 1. The pooled negative LRs for the 3 symptoms are similar: parox-

ysmal cough (LR, 0.52; 95% CI, 0.27-1.0), posttussive emesis (LR, 0.58; 95% CI, 0.44-0.77), and inspiratory whoop (LR, 0.78; 95% CI, 0.66-0.93). In the study that included only children and adolescents (aged 5-16 years),[42] the positive and negative LRs for all symptoms are similar to the pooled positive and negative LRs.

Limitations

No study reported the performance characteristics for combinations of findings (eg, inspiratory whoop together with posttussive emesis) and none evaluated the independence of combinations of findings. Thus, we can only infer that physician clinical impression is affected by presence or absence

Table 1. Study Characteristics

Source	Inclusion Criteria/Setting	No. of Participants	Age, Median (Range), y	Cough Duration at Presentation, Median (Range), d	Reference Standard	Pertussis Prevalence, No. (%) [No. Positive by Each Reference Standard]	Level of Evidence[47,a]
Strebel et al,[44] 2001	Cough 7-34 d; age 10-49 y 10 outpatient clinics (large health maintenance organization), St Paul–Minneapolis, Minnesota	212	35 (10-49)	36 (4-77)	(1) NP specimen using rayon-tipped swab for PCR and culture; (2) ≥2-fold increase in convalescent anti-PT IgG or IgA titers vs acute (antibody ELISA level ≥20 units/mL); (3) single serum anti-PT IgG ≥3 SD above mean for age-matched controls	27 (13) [culture = 8; PCR = 13; acute vs convalescent anti-PT titers = 13; single high anti-PT titer = 18]	III
Park et al,[43] 2005	Cough 1-12 weeks; age ≥16 y 2 outpatient clinics, Seoul, South Korea	102	30 (19-83)	15 (6-80)	Throat swab specimens using Dacron-tipped swab for PCR and culture	3 (2.9) [culture = 0; PCR = 3]	Indeterminate
Harnden et al,[42] 2006	Cough ≥14 d; age 5-16 y General practitioners' clinics, Oxfordshire, England	172	9 (5-16)	Positive serology: mean = 45; negative serology: mean = 44[b]	(1) ≥4-fold change in acute and convalescent serum anti-PT IgG titers (2) anti-PT IgG titers >100 ELISA units/mL	64 (37) [not provided]	I

Abbreviations: ELISA, enzyme-linked immunosorbent assay; NP, nasopharyngeal; PCR, polymerase chain reaction; PT, pertussis toxin.
[a] Levels of evidence: I=highest quality; an independent, blind comparison of a test (pertussis-related symptom) to a validated criterion reference standard in a sufficiently large number of consecutive patients; II=similar to level I (ie, an independent, blind comparison of a test to a validated criterion reference standard) but with a smaller number of patients; III=also independently compared the test with a validated reference standard, but enrolled nonconsecutive patients.
[b] Median and range not reported.

Table 2. Sensitivity, Specificity, and Likelihood Ratios of Classically Described Symptoms in Diagnosing Pertussis

Source	No. (%)		Positive LR (95% CI) [Range]	Negative LR (95% CI) [Range]
	Sensitivity	Specificity		
Paroxysmal cough				
Harnden et al,[42] 2006	55/64 (86)	26/108 (24)	1.1 (0.98-1.3)	0.58 (0.29-1.2)
Park et al,[43] 2005	3/3 (100)	35/99 (35)	1.4 (0.91-2.0)	0.35 (0.03-4.8)
Strebel et al,[44] 2001	27/27 (100)	23/185 (12)	1.1 (1.0-1.2)	0.14 (0.01-2.3)
Summary			1.1 (1.1-1.2) [1.1-1.4][a]	0.52 (0.27-1.0) [0.14-0.58][a]
Posttussive emesis				
Harnden et al,[42] 2006	45/64 (70)	66/108 (61)	1.8 (1.4-2.4)	0.49 (0.32-0.73)
Park et al,[43] 2005	1/3 (33)	82/99 (83)	1.9 (0.37-10)	0.80 (0.36-1.8)
Strebel et al,[44] 2001	15/27 (56)	126/185 (68)	1.7 (1.2-2.6)	0.65 (0.42-1.0)
Summary			1.8 (1.4-2.2) [1.7-1.9][a]	0.58 (0.44-0.77) [0.49-0.80][a]
Inspiratory whoop				
Harnden et al,[42] 2006	32/64 (50)	78/107 (73)	1.8 (1.2-2.7)	0.69 (0.52-0.90)
Park et al,[43] 2005	2/3 (67)	71/99 (72)	2.4 (1.0-5.6)	0.46 (0.09-2.3)
Strebel et al,[44] 2001	7/27 (26)	158/185 (85)	1.8 (0.86-3.7)	0.87 (0.69-1.1)
Summary			1.9 (1.4-2.6) [1.8-2.4][a]	0.78 (0.66-0.93) [0.46-0.87][a]

Abbreviations: CI, confidence interval; LR, likelihood ratio.
[a] I^2 is a test for heterogeneity; less than 25% suggests homogeneity; 25% to 50%, low heterogeneity; 51% to 74%, moderate heterogeneity; and 75% or more, high heterogeneity.[41] For all summary LRs, I^2=0% except negative LR for inspiratory whoop (I^2=4%).

of both posttussive emesis and inspiratory whoop in patients with paroxysmal cough.

Our study's findings must be interpreted in the context of the quality of the included studies, and several points merit consideration. Only 5 studies met our inclusion criteria, and 2 of these were excluded because of methodological limitations. Only 1 of the 3 included studies[42] contained level I evidence[47]; the 3 studies had a total of 94 cases of pertussis. One study[44] met level III evidence criteria because of nonconsecutive enrollment and inclusion of a small percentage of eligible patients (2%). The evidence level for the remaining study[43] could not be determined from the article, although that study included only 3 patients with pertussis and, thus, had little effect on the summary measures. Because of the heterogeneity in the patient populations (eg, age ranges of patients, countries of origin) and reference standards used, combining the results of the studies may not be appropriate. Despite these differences in the studies, the quantitative assessments suggested little heterogeneity in the results and the summary measures provide relatively narrow 95% CIs.

Misclassification bias may have affected the performance characteristics we measured. No studies described the use of explicit and reproducible definitions for each symptom. In 1 study,[42] the authors reported that half of patients with a positive serologic test result for pertussis had inspiratory whoop, but they subsequently indicated that few had "classical whoop." For the symptom of paroxysmal cough, it is possible that eliciting a history of coughing fits in a single expiration followed by deep inspiration, rather than undefined "paroxysmal cough," could have resulted in a higher positive LR.

An inclusion criterion for 1 study[44] was paroxysmal cough, which was also one of the findings reported in the study—this represents verification bias.[38] Additionally, patients in this study who were subsequently diagnosed as having pneumonia or sinus-

itis (numbers not given) were excluded from analysis rather than being counted in the nonpertussis group. Both of these factors may falsely increase sensitivity and decrease specificity.

Finally, the limitations of available diagnostic tests (ie, our chosen reference standards) continue to make the diagnosis of pertussis challenging. The sensitivity of these diagnostic tests decreases with increased duration of cough and, as noted, adolescents and adults often do not seek medical attention until they have been coughing for several weeks. This problem with the reference standard may in turn affect our assessment of the diagnostic utility of the classic symptoms.

SCENARIO RESOLUTION

A nasopharyngeal swab specimen was collected from the patient and sent for testing. The estimated pretest probability of pertussis for an adult with a prolonged cough is 10% to 30%. The presence of posttussive emesis (LR, 1.8) modestly increases the posttest probability. For this patient, the direct fluorescent antibody test result was negative, but *B pertussis* was isolated from culture 1 week later. Four weeks after the onset of illness, when the culture result was reported, treatment with oral erythromycin was started. The patient's cough gradually resolved over the next 3 months. Because of her frequent and prolonged exposure to the patient, his wife was given postexposure antibiotic prophylaxis; she did not develop symptoms of pertussis infection.

CLINICAL BOTTOM LINE

In the prevaccine era, 4 symptoms were classically associated with pertussis infection: paroxysmal cough, posttussive emesis, posttussive syncope, and inspiratory whoop. Although a prolonged duration of cough illness is also characteristic of pertussis, we were unable to find any studies with extractable data to assess this. Our systematic review of the literature included 3 nonoutbreak studies in the postvaccine era of patients seeking care for cough that included data on paroxys-

mal cough, posttussive emesis, and inspiratory whoop; no study reported on posttussive syncope. Paroxysmal cough is a very common symptom in pertussis infection, but it appears to be nonspecific (ie, paroxysmal cough may also commonly occur in other respiratory illnesses). The presence of posttussive emesis and inspiratory whoop modestly increase the likelihood of pertussis infection, but additional information should influence the decision to test and empirically treat for pertussis. This should include recent exposure to known or suspected cases of pertussis and subsequent exposure to vulnerable populations (eg, infants). Importantly, our data do not apply to an outbreak setting in which the pretest probability of pertussis for a patient with a cough illness may be substantially higher and the thresholds to test and empirically treat for pertussis may be lower.

Given the substantial limitations of currently available diagnostic tests, an important finding in this study is that the absence of classic symptoms of pertussis may not have sufficiently low LRs to exclude the diagnosis of pertussis, and the presence of classic symptoms is common in patients who do not have evidence of pertussis infection. This increases the importance of the pretest probability of infection and suggests that additional testing and treatment decisions in a patient with prolonged cough should be based on the overall clinical impression, independent of these classic clinical features of pertussis. Studies including adolescents and adults with cough illnesses lasting 1 week or longer in nonoutbreak settings indicate that pertussis is responsible for 12% to 32% of cases; the overwhelming majority of patients actually had a substantially longer duration of illness (>3 weeks).[14] We suspect that most experts consider the combination of a whooping cough and posttussive emesis more suggestive of the diagnosis than either finding alone. Future investigations that provide data on the combinations of findings may be useful.

REFERENCES

1. Lambert HJ. Epidemiology of a small pertussis outbreak in Kent County, Michigan. *Public Health Rep*. 1965;80:365-369.
2. Jenkinson D. Duration of effectiveness of pertussis vaccine: evidence from a 10 year community study. *Br Med J (Clin Res Ed)*. 1988;296(6622):612-614.
3. Dworkin MS. Adults are whooping, but are internists listening? *Ann Intern Med*. 2005;142(10):832-835.
4. Hewlett EL, Edwards KM. Pertussis—not just for kids. *N Engl J Med*. 2005;352(12):1215-1222.
5. Irwin RS. Complications of cough: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1)(suppl):54S-58S.
6. Irwin RS. Introduction to the diagnosis and management of cough: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1)(suppl):25S-27S.
7. Irwin RS, Madison JM. The diagnosis and treatment of cough. *N Engl J Med*. 2000;343(23):1715-1721.
8. Pratter MR, Brightling CE, Boulet LP, Irwin RS. An empiric integrative approach to the management of cough: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1)(suppl):222S-231S.
9. Kwon NH, Oh MJ, Min TH, Lee BJ, Choi DC. Causes and clinical features of subacute cough. *Chest*. 2006;129(5):1142-1147.
10. Pratter MR. Overview of commons causes of chronic cough: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1)(suppl):59S-62S.
11. Gibson PG, Dolovich J, Denburg J, Ramsdale EH, Hargreave FE. Chronic cough: eosinophilic bronchitis without asthma. *Lancet*. 1989;1(8651):1346-1348.
12. Brightling CE, Ward R, Goh KL, Wardlaw AJ, Pavord ID. Eosinophilic bronchitis is an important cause of chronic cough. *Am J Respir Crit Care Med*. 1999;160(2):406-410.
13. Mattoo S, Cherry JD. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to *Bordetella pertussis* and other Bordetella subspecies. *Clin Microbiol Rev*. 2005;18(2):326-382.
14. von König CH, Halperin S, Riffelmann M, Guiso

N. Pertussis of adults and infants. *Lancet Infect Dis*. 2002;2(12):744-750.
15. Fine PEM. Adult pertussis: a salesman's dream—and an epidemiologist's nightmare. *Biologicals*. 1997;25(2):195-198.
16. Centers for Disease Control and Prevention. Pertussis—United States, 1997-2000. *MMWR Morb Mortal Wkly Rep*. 2002;51(4):73-76.
17. Centers for Disease Control and Prevention. Pertussis—United States, 2001-2003. *MMWR Morb Mortal Wkly Rep*. 2005;54(50):1283-1286.
18. McNabb SJ, Jajosky RA, Hall-Baker PA, et al; Centers for Disease Control and Prevention. Summary of notifiable diseases—United States, 2006. *MMWR Morb Mortal Wkly Rep*. 2008;55(53):1-92.
19. Broder KR, Cortese MM, Iskander JK, et al; Advisory Committee on Immunization Practices. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-3):1-34.
20. Kretsinger K, Broder KR, Cortese MM, et al; Centers for Disease Control and Prevention; Advisory Committee on Immunization Practices; Healthcare Infection Control Practices Advisory Committee. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR Recomm Rep*. 2006;55(RR-17):1-37.
21. Güriş D, Strebel PM, Bardenheier B, et al. Changing epidemiology of pertussis in the United States: increasing reported incidence among adolescents and adults, 1990-1996. *Clin Infect Dis*. 1999;28(6):1230-1237.
22. Edwards KM. Overview of pertussis: focus on epidemiology, sources of infection, and long term protection after infant vaccination. *Pediatr Infect Dis J*. 2005;24(6)(suppl):S104-S108.
23. Tanaka M, Vitek CR, Pascual FB, Bisgard KM, Tate JE, Murphy TV. Trends in pertussis among infants in the United States, 1980-1999. *JAMA*. 2003;290(22):2968-2975.
24. Vitek CR, Pascual FB, Baughman AL, Murphy TV. Increase in deaths from pertussis among young infants in the United States in the 1990s. *Pediatr Infect Dis J*. 2003;22(7):628-634.
25. Cherry JD, Grimprel E, Guiso N, Heininger U, Mertsola J. Defining pertussis epidemiology: clinical, microbiologic and serologic perspectives. *Pediatr Infect Dis J*. 2005;24(5)(suppl):S25-S34.
26. Müller FM, Hoppe JE, Wirsing von König CH. Laboratory diagnosis of pertussis: state of the art in 1997. *J Clin Microbiol*. 1997;35(10):2435-2443.
27. Cornia PB, Lipsky BA, Saint S, Gonzales R. Nothing to cough at—a 73-year-old man presented to the emergency department with a 4-day history of nonproductive cough that worsened at night. *N Engl J Med*. 2007;357(14):1432-1437.
28. Centers for Disease Control and Prevention. Guidelines for the control of pertussis outbreaks. 2000. http://www.cdc.gov/vaccines/pubs/pertussis-guide/guide.htm. Accessed April 8, 2010.
29. Young S, Anderson G, Mitchell P. Laboratory observations during an outbreak of pertussis. *Clin Microbiol Newsl*. 1987;9:176-179.
30. Lievano FA, Reynolds MA, Waring AL, et al. Issues associated with and recommendations for using PCR to detect outbreaks of pertussis. *J Clin Microbiol*. 2002;40(8):2801-2805.
31. Gonzales R, Bartlett JG, Besser RE, et al; Ameri-

can Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine; Centers for Disease Control; Infectious Diseases Society of America. Principles of appropriate antibiotic use for treatment of uncomplicated acute bronchitis: background. *Ann Intern Med*. 2001;134(6):521-529.
32. Tiwari T, Murphy TV, Moran J; National Immunization Program, Centers for Disease Control and Prevention. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines. *MMWR Recomm Rep*. 2005;54(RR-14):1-16.
33. Aoyama T, Sunakawa K, Iwata S, Takeuchi Y, Fujii R. Efficacy of short-term treatment of pertussis with clarithromycin and azithromycin. *J Pediatr*. 1996;129(5):761-764.
34. Langley JM, Halperin SA, Boucher FD, Smith B; Pediatric Investigators Collaborative Network on Infections in Canada. Azithromycin is as effective as and better tolerated than erythromycin estolate for the treatment of pertussis. *Pediatrics*. 2004;114(1):e96-e101.
35. Lebel MH, Mehra S. Efficacy and safety of clarithromycin versus erythromycin for the treatment of pertussis: a prospective, randomized, single blind trial. *Pediatr Infect Dis J*. 2001;20(12):1149-1154.
36. Pichichero ME, Hoeger WJ, Casey JR. Azithromycin for the treatment of pertussis. *Pediatr Infect Dis J*. 2003;22(9):847-849.
37. Centers for Disease Control and Prevention. Pertussis (*Bordetella pertussis*) (whooping cough): 2010 case definition. http://www.cdc.gov/ncphi/disss/nndss/casedef/pertussis_Current.htm. Accessed June 30, 2010.
38. Newman TB, Kohn MA. *Evidence-Based Diagnosis.* New York, NY: Cambridge University Press; 2009:99-101.
39. Centers for Disease Control and Prevention. Outbreaks of respiratory illness mistakenly attributed to pertussis—New Hampshire, Massachusetts, and Tennessee, 2004-2006. *MMWR Morb Mortal Wkly Rep*. 2007;56(33):837-842.
40. Simel DL, Bossuyt PM. Differences between univariate and bivariate models for summarizing diagnostic accuracy may not be large. *J Clin Epidemiol*. 2009;62(12):1292-1300.
41. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
42. Harnden A, Grant C, Harrison T, et al. Whooping cough in school age children with persistent cough: prospective cohort study in primary care. *BMJ*. 2006;333(7560):174-177.
43. Park WB, Park SW, Kim HB, Kim EC, Oh M, Choe KW. Pertussis in adults with persistent cough in South Korea. *Eur J Clin Microbiol Infect Dis*. 2005;24(2):156-158.
44. Strebel P, Nordin J, Edwards K, et al. Population-based incidence of pertussis among adolescents and adults, Minnesota, 1995-1996. *J Infect Dis*. 2001;183(9):1353-1359.
45. Centers for Disease Control and Prevention. National, state, and local area vaccination coverage among children aged 19-35 months—United States, 2007. *MMWR Morb Mortal Wkly Rep*. 2008;57(35):961-966.
46. Wirsing von König CH, Campins-Marti M, Finn A, Guiso N, Mertsola J, Liese J. Pertussis immunization in the global pertussis initiative European region: recommended strategies and implementation considerations. *Pediatr Infect Dis J*. 2005;24(5)(suppl):S87-S92.
47. Simel DL. Update: primer on precision and accuracy. In: Simel DL, Rennie D, eds. *The Rational Clinical Examination: Evidence-Based Clinical Diagnosis.* New York, NY: McGraw-Hill; 2008:9-16.