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Sensitivity and Specificity of Clinical Case Definitions for Pertussis

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Abstract: We evaluated the diagnostic performance of 15 clinical case definitions for pertussis in 233 patients who developed acute respiratory illness during community outbreaks in Wisconsin and Delaware. Using results from culture (Regan-Lowe media) and serology (Ig-class-specific ELISA) as diagnostic standards, cough for ≥14 days was both sensitive (84 per cent–92 per cent) and specific (63 percent–90 per cent) in identifying patients with pertussis. This definition may be useful in monitoring pertussis outbreaks and for investigating contacts of culture-positive cases. (*Am J Public Health* 1988; 78:833–836.)

Introduction

Advances in our understanding of the occurrence, prevention, and control of *Bordetella pertussis* infections have been impeded by difficulties in diagnosis.[1,2] Although isolation of the organism is widely accepted as the most specific criterion, current culture methods have also been shown to be relatively insensitive, costly, and labor-intensive.[3] These limitations may be overcome to some extent by fluorescent-antibody staining of nasopharyngeal secretions (DFA),[3] but the specificity of this technique is highly variable, even in the hands of experienced personnel.[4] While preliminary studies of newer serologic assays are encouraging,[3] limited availability and the necessity for obtaining paired specimens for adequate interpretation currently preclude these tests from being used routinely. Although a standard clinical case definition would provide a simple and uniform method for diagnosis and reporting, pertussis is often modified by prior vaccination and is infrequently accompanied by classical features such as whoop or post-tussive vomiting.[1-3]

In 1985 and 1986, community outbreaks of pertussis occurred in Wisconsin and Delaware, respectively, in which a large number of cases were confirmed by culture and/or serology. Using the results of these tests as diagnostic standards, we evaluated the frequency and duration of signs and symptoms in 233 patients to determine whether a sensitive and specific clinical case definition for pertussis could be developed.

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Methods

Wisconsin

In the period July–November 1985, an outbreak of pertussis was identified in a three-county region in Central Wisconsin, with more than 95 per cent of cases reported by a single medical care facility (the Marshfield Clinic). Nasopharyngeal swabs were collected from all patients who presented with symptoms of acute respiratory illness and from all household contacts who were present at the time of the examination. Specimens were transported to the laboratory in tubes containing half-strength Oxoid charcoal agar supplemented with 10 per cent defibrinated horse blood and 40 μg/ml of cephalexin (Regan-Lowe)[5] and processed within 24 hours. Full-strength Regan-Lowe plates were used for primary isolation of *Bordetella pertussis*.

In December 1985, a standardized questionnaire was administered by telephone to collect demographic and clinical information from all culture-positive patients who had been identified during the preceding two-month period. Similar information was obtained from all symptomatic, but culture-negative household contacts. The number of doses of DTP (diphtheria, tetanus, pertussis) vaccine that each person had received (usually based on recall) was also recorded, as well as a history of having taken erythromycin or other antibiotics during the acute phases of illness.

Delaware

In the period March–May 1986, an outbreak of pertussis was identified in a rural community in Delaware. In late April, 50 homes were visited to collect nasopharyngeal swabs and serum specimens from all consenting household members and to record the date of onset and duration of acute respiratory symptoms that had developed during the preceding month. Similar data (as well as convalescent sera) were collected during a follow-up visit six weeks later, using the same forms that had been used in Wisconsin. Nasopharyngeal specimens were processed using methods identical to those used in Wisconsin, except that full-strength Regan-Lowe plates were inoculated directly. Only those persons who manifested symptoms of acute respiratory illness during the 10-week reference period and whose culture was obtained within the two-week period before or after their symptoms began were included in the analysis.

Serologic Testing

All serum specimens collected in Delaware were tested for the presence of antibody against purified filamentous hemagglutinin (FHA) and pertussis toxin (PT) antigens of *B. pertussis* using an Ig-class-specific enzyme-linked immuno-

TABLE 1—Sensitivity, Specificity, and Predictive Values of Clinical Case Definitions for Pertussis (compared with culture results), Central Wisconsin (1985) and Kent County, Delaware (1986)

Clinical Manifestation (Case Definition)	No. Patients in cell* A	B	C	D	Sensitivity (95% CI)	Specificity (95% CI)	Predictive Value + (95% CI)	Predictive Value − (95% CI)
Any symptom or sign of acute respiratory illness	118	115	0	0	100	0	51 (44,57)	N.A.
Acute cough of any duration	116	83	2	32	98 (96,100)	28 (20,36)	58 (51,65)	94 (86,100)
Cough for ≥14 days	99	43	19	72	84 (77,91)	63 (54,71)	70 (62,77)	79 (71,87)
Paroxysmal cough for ≥7 days	64	26	54	89	54 (45,63)	77 (70,85)	71 (62,80)	62 (54,70)
Paroxysmal cough resulting in sleep disturbance†	65	25	53	90	55 (46,64)	78 (71,86)	72 (63,81)	63 (55,71)
Paroxysmal cough for ≥7 days or sleep disturbance	77	35	41	80	65 (57,74)	70 (61,78)	69 (60,77)	66 (58,75)
Cough for ≥14 days and paroxysms	61	19	57	96	52 (43,61)	83 (77,90)	76 (67,86)	63 (55,70)
Cough for ≥14 days and sleep disturbance	60	18	58	97	51 (42,60)	84 (78,91)	77 (68,86)	63 (55,70)
Cough for ≥14 days and paroxysms and sleep disturbance	50	14	68	101	42 (33,51)	88 (82,94)	78 (68,88)	60 (52,67)
Cough for ≥14 days and paroxysms and fever	17	3	101	112	14 (8,21)	97 (94,100)	85 (69,100)	53 (46,59)
Cough for ≥14 days and sleep disturbance and fever	16	4	102	111	14 (7,20)	97 (93,100)	80 (62,98)	52 (45,59)
Cough for ≥14 days and paroxysms and sleep disturbance and fever	14	3	103	112	12 (6,18)	97 (94,100)	82 (64,100)	52 (45,59)
Cough for ≥14 days or paroxysmal cough for ≥7 days	102	50	16	65	86 (80,93)	57 (47,66)	67 (60,75)	80 (72,89)
Cough for ≥14 days or sleep disturbance	104	50	14	65	88 (82,94)	57 (47,66)	68 (60,75)	82 (74,91)
Cough for ≥14 days or paroxysmal cough or sleep disturbance	105	55	13	60	89 (83,95)	52 (43,61)	66 (58,73)	82 (73,91)

*Values for sensitivity, specificity, positive predictive value and negative predictive value were calculated according to the following 2×2 table and accompanying formulas[8]:

		Culture Results pos	neg	
				Sensitivity = A/(A+C)
	pos	A	B	Specificity = D/(D+B)
Clinical symptom/sign				Predictive Value Positive = A/(A+B)
	neg	C	D	Predictive Value Negative = D/(C+D)

†"Sleep disturbance" refers to patient waking on ≥2 consecutive nights from paroxysms of coughing.

sorbent assay (ELISA).[6] Analysis was restricted to paired sera in which: 1) the first (acute-phase) specimen had been collected within seven days after onset of symptoms (25 patients) or within 14 days after exposure to the index patient in the same household (10 controls); and 2) the second (convalescent-phase) specimen had been collected more than two weeks after symptom onset (for patients) or more than three weeks after exposure to the index patient (for controls).[7] Two-fold or greater rises in antibody titer against FHA or PT in paired sera were considered diagnostic of infection, based on earlier evaluations of the performance and sensitivity of the assay.[6,7]

Analysis

Standard formulas were used to determine the sensitivity and specificity (and 95% confidence interval [CI]) with which a given symptom complex predicted: 1) a positive culture for *B. pertussis;* or 2) a ≥2-fold rise in antibody titer (see footnotes in tables). Since whoop and post-tussive vomiting were reported by less than 5 per cent of patients from Wisconsin, comparisons were restricted to the signs and symptoms listed in Table 1.

Results

Diagnostic Standard = Culture Results

A total of 233 persons were included in the analysis, including 111 (48 per cent) from Wisconsin and 122 (52 per cent) from Delaware. One-hundred-sixteen (50 per cent) of the illnesses were culture-positive and 117 (50 per cent) were culture-negative, with the mean interval between the date of onset of the first symptom and the date of specimen collection being similar in both groups (6.7 days vs 5.0 days, respectively; $p > .1$, Wilcoxon rank sum test); none of the 233 patients were taking antibiotics at the time that cultures were obtained. Since there were no differences in the diagnostic accuracy of clinical case definitions between Wisconsin and Delaware,* the data were combined for purposes of presentation in this report.

As shown in Table 1, the presence of *any* acute respiratory symptom—which included cough, coryza, nasal congestion, *or* sore throat—was, by definition, 100 per cent sensitive but 0 per cent specific in identifying patients with pertussis. The addition of cough increased the specificity of diagnosis to 28 per cent, with only a negligible change in sensitivity. When duration of cough (14 days or more) was also included in the definition, specificity rose significantly (to 63 per cent), with only a modest decline in sensitivity (to 84 per cent). Definitions requiring paroxysmal cough increased the specificity of diagnosis by as much as 25 per cent—with concomitant, but more modest, increases in predictive value positive—but were also accompanied by large reductions in sensitivity (Table 1). Definitions using combinations of cough for ≥14 days or paroxysmal cough offered no substantial improvements in diagnostic accuracy compared with the more simple definition of cough for ≥14 days alone.

To determine whether values for sensitivity, specificity, and predictive value might vary with the age of the patient, participants in the study were stratified according to the following age groups: those less than 5 years of age (n = 69); those age 5 through 14 (n = 86); those age 15 years or older (n = 78). Although specificities and positive predictive values tended to be higher for persons age 5 years or older than for younger children, differences were small. Similarly, only minor changes were also observed when patients were stratified according to: 1) the interval between onset of illness and specimen collection; 2) whether they had taken antibiotics during their illness; or 3) whether they had previously received three or more doses of DTP vaccine (analysis confined to children age 6 mo–14 yr).

*Data available on request to author.

TABLE 2—Diagnositic Performance of Selected Clinical Case Definitions for Pertussis Using Serologic Results as the Diagnostic Standard

Case Definition/Serologic Test	No. Patients in cell* A	B	C	D	Sensitivity (95% CI)	Specificity (95% CI)	Predictive Value + (95% CI)	Predictive Value − (95% CI)
Cough for ≥14 days/IgG-FHA	10	1	1	9	91 (74,100)	90 (71,100)	91 (74,100)	90 (71,100)
Cough for ≥14 days/IgG-PT	9	2	2	8	82 (59,100)	80 (55,100)	82 (59,100)	80 (55,100)
Cough for ≥14 days/IgA-FHA	8	3	1	9	89 (68,100)	75 (51,100)	73 (46,99)	90 (71,100)
Cough for ≥14 days/IgA-PT	9	2	1	9	90 (71,100)	82 (59,100)	82 (59,100)	90 (71,100)
Cough for ≥14 days or paroxysmal cough/IgG-FHA	11	4	1	9	92 (76,100)	69 (44,94)	73 (51,96)	90 (71,100)
Cough for ≥14 days or paroxysmal cough/IgG-PT	12	3	2	8	86 (67,100)	73 (46,99)	80 (60,100)	80 (55,100)
Cough for ≥14 days or paroxysmal cough/IgA-FHA	10	5	1	9	91 (74,100)	64 (39,89)	67 (43,91)	90 (71,100)
Cough for ≥14 days or paroxysmal cough/IgA-PT	11	4	1	9	92 (76,100)	69 (44,94)	73 (51,96)	90 (71,100)
URI† only/IgG FHA	1	9	1	9	50 (0,100)	50 (27,73)	10 (0,29)	90 (71,100)
URI only/IgG-PT	2	8	2	8	50 (1,99)	50 (26,75)	20 (0,45)	80 (55,100)
URI only/IgA-FHA	1	9	1	9	50 (0,100)	50 (27,73)	10 (0,29)	90 (71,100)
URI only/IgA-PT	1	9	2	8	33 (0,87)	47 (23,71)	10 (0,29)	80 (55,100)

*Values for sensitivity, specificity, positive predictive value and negative predictive value were calculated according to the following 2×2 table and accompanying formulas[8]:

		≥2-fold rise in Ab yes	no	
				Sensitivity = A/(A+C)
	pos	A	B	Specificity = D/(D+B)
Clinical symptom/sign				Predictive Value Positive = A/(A+B)
	neg	C	D	Predictive Value Negative = D/(C+D)

†URI refers to coryza, sore throat, or cough lasting <14 days. Comparison group in this analysis (i.e., patients listed in cells C and D) consists of asymptomatic household contacts.

Diagnostic Standard = Serologic Results

The diagnostic performance of selected clinical case definitions for pertussis compared with IgG and IgA results is presented in Table 2. Although the number of patients included in these comparisons was small, point estimates for specificity and positive predictive value were considerably higher than those presented in Table 1, particularly for the definition of cough for ≥14 days. These differences were best explained by differences in sensitivity between the two diagnostic standards, with culture being only one-half to two-thirds as sensitive as serology (data not shown). IgM results were neither sensitive nor specific in diagnosing pertussis, consistent with observations reported earlier.[7]

IgG and IgA responses in patients with cough for ≥14 days were also compared with responses in patients with mild illnesses, as well as those in asymptomatic household contacts. Whereas the percentage of serologically confirmed infections in patients with mild illness was generally low (10–20 per cent)—and virtually identical to the percentage in asymptomatic contacts (see Table 2)—10 (91 per cent) of the 11 patients with cough for ≥14 days demonstrated a ≥2-fold rise in antibody in at least one of the assays ($p < .003$).

Discussion

The results of this investigation confirm the impression that the clinical spectrum of pertussis is changing in an era in which nearly all children and adolescents and many young adults have received three or more doses of DTP vaccine. Since classical manifestations such as whoop and post-tussive vomiting are usually present in only a small proportion of patients, more than half of all state health departments require laboratory confirmation before accepting a physician-diagnosed case.[9] Reliance on laboratory diagnosis contributes to inconsistency and underreporting of pertussis,[1] overestimates its rates of complications,[1] and may also impair the ability to investigate, monitor, and control community outbreaks. It seems clear that other diagnostic criteria would be useful, particularly when cultures are not obtained or when the organism fails to be isolated in spite of epidemiologic linkages to culture-confirmed cases.

The present study suggests that a case definition of acute cough lasting ≥14 days would provide a sensitive and uniform approach for monitoring the course of laboratory-proven outbreaks of pertussis and for purposes of investigating contacts of culture-positive cases. This definition can be applied to patients of all ages, regardless of prior vaccination or antimicrobial therapy during the symptomatic phases of illness.[8] While the specificity and positive predictive value of this definition were somewhat low when culture results were used as the diagnostic standard, evaluations using the more sensitive standard, ELISA, suggest that its true specificity and predictive value are probably higher. Nevertheless, in circumstances in which high specificity is of paramount importance—such as accurate estimation of vaccine efficacy—subgroups of cases meeting the more rigorous definitions in Table 1 could be analyzed separately.

While it appears to be useful in outbreak settings, the performance of a case definition of cough for ≥14 days in diagnosing sporadic cases of pertussis is unknown. Because pertussis remains a relatively uncommon disease in the United States, and because there are a number of other conditions which may be characterized by prolonged cough, the positive predictive value of cough for ≥14 days is likely to be lower when used for this purpose. In addition, because a diagnosis based on this case definition cannot be made until the later stages of infection, other signs and symptoms such as paroxysmal cough will have to be used to identify suspect cases and to guide decisions about antimicrobial therapy and prophylaxis.

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Determination of Immune Status to Measles, Rubella, and Varicella-Zoster Viruses among Medical Students: Assessment of Historical Information

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Abstract: We examined the serological susceptibility of entering medical students to measles, rubella, and varicella-zoster (VZV) viruses over a four-year period. Serological results were then compared to historical information to ascertain whether undocumented histories of disease or vaccination could be used to identify students who may not need serological testing. For measles, historical information was of no benefit in predicting immunity. For VZV and, to a greater extent, rubella, a higher seropositive rate was seen in students claiming a positive history. (*Am J Public Health* 1988; 78:836–838.)

Introduction

Outbreaks of measles and rubella infections continue to occur sporadically in the United States on college campuses and in health care settings.[1,2] Among adolescent and young adult populations,[3] susceptibility levels of 5–10 per cent for measles virus, and 10–20 per cent for rubella virus are similar to those of pre-vaccine years. Studies suggest that 8 per cent of persons over 20 years of age may be susceptible to varicella-zoster virus.[4]

Medical students—representing a small proportion of the young adult population—may be especially exposed to these infections in college and hospital environments. Poor physician participation has hampered hospital screening programs in the past.[5] Identifying and immunizing susceptible medical students may also assist the completion of such screening programs in the future.

We have determined the serological susceptibility to measles, rubella, and varicella-zoster (VZV) viruses in students entering two Michigan medical schools. Because our nationwide survey[6] indicated that many medical schools rely upon historical information alone to identify susceptibles, we assessed the role of the undocumented history when screening this population.

Methods

Entering students attending the College of Human Medicine and the College of Osteopathic Medicine at Michigan State University (MSU) completed questionnaires which dealt with past history of diseases and vaccinations. Responses were recorded as "yes", "no", or "don't know". A sample of blood was requested from each student who provided a history form. Antibody titers were performed using a hemagglutination inhibition (HI) technique for rubella,[7] and immune adherence hemagglutination (IAHA)[8] for measles and varicella-zoster viruses. Titers < 1:8, obtained by HI or IAHA, were considered negative (non-immune).

Immune status to measles was also evaluated on selected sera by an enzyme-linked immunosorbent assay (ELISA), Enzygnost®-Measles (Behringwerke AG, Marburg, West Germany). Testing for measles antibody by this method and by IAHA has been compared with plaque neutralization (PNt—performed by Dr. Paul Albrecht, Bureau of Biologics, Food and Drug Administration, Bethesda, MD).[9] In testing 35 coded samples, the ELISA method proved more sensitive than IAHA, while equally specific.*

VZV antibody was also determined on a group of selected sera by VARICELISA® (M.A. Bioproducts, Walkersville, MD). Previous studies have demonstrated excellent sensitivity and specificity of an ELISA method in comparison with fluorescent antibody to membrane antigen or plaque neutralization to determine VZV immune status.[10,11]

For ELISA determinations, frozen (−70° C) sera, from the original phlebotomy, not previously thawed, were used. All ELISA testing was performed according to manufacturers' instructions. Final dilution of serum for Enzygnost®-Measles was 1:44 and, for VARICELISA®, 1:26. Absorbance values (A) were obtained at a wavelength of 405nm, with positive cutoff absorbance values predetermined by the

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