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Should the Pertussis Case Definition for Public Health Reporting Be Refined?

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Abstract

Background—The surveillance case definition for confirmed pertussis requires that an individual with a positive polymerase chain reaction (PCR) for *Bordetella pertussis* have $\geq$ two weeks of cough and at least one of the following: paroxysmal coughing, inspiratory “whoop,” or post-tussive vomiting.

Objectives—Determine 1) proportion of individuals with a positive PCR who met additional criteria for surveillance confirmed pertussis, 2) whether the likelihood of PCR positive individuals meeting additional elements of surveillance case definition varied by age or vaccination status, and 3) whether elements of the current case definition influence the likelihood of pertussis confirmation in PCR positive individuals.

Methods—Pertussis PCR results were compared with case investigation data.

Results—165/188 (88%) PCR positive individuals met requirements for confirmed pertussis. 61% (14/23) of PCR positive individuals who had $<$ two but $>$ one week of cough had at least one other reported sign or symptom. 14(100%) reported paroxysmal coughing, seven (50%) “whoop,” and seven (50%) post-tussive vomiting. Infants who met case definition were more likely to have reported apnea than older individuals (15/17 vs. 45/86, OR 6.8, 95% CI 1.4–64.2).

Conclusions—Decreasing cough duration from $\geq$ two weeks to $>$ one week would result in 95% of those with positive PCR meeting confirmation criteria for pertussis. Apnea should be considered an additional sign for pertussis confirmation in infants.

Keywords

Bordetella pertussis; polymerase chain reaction; public health practice

INTRODUCTION

Disease surveillance is a critical and long-standing public health function. Pertussis surveillance is of particular importance because it is a cyclical disease with a recent striking increase in the incidence of reported cases in 2004–2005. Although total reported pertussis cases decreased in the United States in 2006, the reported rate of pertussis in infants under 6

months of age, the age group with the greatest morbidity and mortality, remained highest at 84.2 per 100,000 population.¹ Considerable public health resources are targeted at controlling pertussis. Since 1979, local and state public health departments have collected and reported detailed clinical, demographic, and laboratory data on pertussis cases. In response to reported pertussis cases, public health personnel implement control measures, classify cases according to surveillance case definition, and report information about probable and confirmed cases to the National Notifiable Disease Surveillance System at the Centers for Disease Control (CDC) and Prevention.²

The current case definition for pertussis surveillance was adopted in 1997 by the Council of State and Territorial Epidemiologists and the CDC.³ While the previous case definition (1994) allowed confirmation of disease based on the presence of cough of any duration and isolation of *B. pertussis* from a clinical specimen,⁴ the 1997 revision mandated that one of the following conditions be met for a case to be confirmed: 1) positive culture and a cough illness of any duration 2) positive PCR, at least two weeks of cough, and at least one additional clinical criterion or 3) two weeks of cough, at least one additional clinical criteria, and direct epidemiological linkage to a case confirmed by either culture or PCR.^{5,6} If an individual with a positive PCR does not have a reported symptom that meets one of the clinical criteria, the case is not counted as confirmed by the surveillance system.

Case definitions are often intentionally restrictive to ensure consistency in surveillance data across jurisdictions and over time and it is well recognized that not all persons with clinically significant disease will meet criteria for reporting to a surveillance system.⁷ In addition, variations in reporting, underreporting, and the stringent surveillance case definition may result in an underestimation of the true prevalence of pertussis.^{8,9} Surveillance data from the Utah Department of Health (UDOH) demonstrated that in 2006 Utah had the highest state-specific rate (31.5 per 100,000) in the nation and the second highest rate in 2007 (15.2 per 100,000).^{10,11} From 2000 to 2006, the rate of reported pertussis cases in Utah increased from 2.0 per 100,000 population per year to 31.5 per 100,000 population per year.¹⁰ Although increased rates were reported in all age groups and infants continue to have the highest morbidity, the greatest increase in reported cases in Utah in the last decade has been in the adolescent and adult populations.¹² PCR use also rapidly increased between 2003 and 2005, and in Utah has replaced culture as the most frequently used laboratory method for diagnosis of pertussis in children.¹²

PCR has become widely available as a diagnostic tool for pertussis. PCR is a rapid, sensitive, and inexpensive test for diagnosing pertussis and may provide more accurate and timely information regarding its true prevalence.^{13–15} While an increasing number of laboratories provide PCR for confirmatory testing, there are limited data to indicate whether individuals with a positive PCR also meet the surveillance case definition for confirmed pertussis. The goals of this study were to determine 1) proportion of individuals with a positive PCR who met additional criteria for surveillance confirmed pertussis, 2) whether the likelihood of PCR positive individuals meeting additional elements of surveillance case definition varied by age or vaccination status, and 3) whether elements of the current case definition influence the likelihood of pertussis confirmation in PCR positive individuals.

METHODS

Protection of Human Subjects

Approval to conduct this study was granted by the Institutional Review Boards of the University of Utah and Intermountain Healthcare (Intermountain) in Salt Lake City, Utah. The Utah Department of Health participated in this project in order to assess and improve statewide investigation and reporting procedures.

PCR Testing at Intermountain

Intermountain Healthcare is the largest provider of healthcare in the Intermountain West with over 160 facilities. Intermountain maintains a single centralized PCR laboratory that performs all of the PCR testing for Intermountain hospitals and clinics. The real-time PCR assay for *Bordetella pertussis* utilizes the ABI Prism 7000 Sequence Detection System. The *B. pertussis* target sequence is IS481 nucleotides 33 to 112.¹⁶ Internal positive and negative controls are included for each reaction and are tested in the same manner, at the same time, and by the same person as patient samples to assure quality control of the purification run. This assay cannot distinguish *B. pertussis* from *B. holmseii*.

Identification of PCR Positive Subjects from Intermountain and Utah Department of Health

Intermountain began PCR testing for pertussis at its central laboratory in November, 2004. We queried the Intermountain Enterprise Data Warehouse (EDW) for all individuals tested for pertussis by PCR at all Utah Intermountain facilities from November, 2004 to June, 2006. We then queried the Utah Department of Health (UDOH) National Electronic Telecommunications System for Surveillance (NETSS) database for all reported PCR positive pertussis cases from Intermountain Healthcare facilities during the same time period.

Clinical Data from IH

The EDW database query ascertained the following information for each patient: testing facility, test date, test result and age at the time test was performed. Additional clinical information was obtained by review of the EDW linked medical records and included admitting and discharge diagnoses.

UDOH Case Investigation

The NETSS database was queried for reported pertussis cases with positive PCR tests performed at Utah Intermountain facilities. The data was correlated with case investigation reports to determine which PCR positive cases met the additional criteria for the surveillance definition of a confirmed pertussis case. The 1997 surveillance case definition for confirmed pertussis based on positive PCR testing requires cases to have “a cough illness lasting at least two weeks with one or more of the following: paroxysms of coughing, inspiratory “whoop,” or post-tussive vomiting without other apparent cause (as reported by a health professional).”⁵ Although the surveillance case definition does not include apnea as an associated sign or symptom, UDOH collects data on apnea for reported pertussis cases.

Statistical Analysis

Data were managed using Microsoft Access and analyzed using Stata Version 10.0. Individuals were categorized by age groups commonly used by UDOH to summarize surveillance data: <1, 1–4, 5–14, 15–24, 25–44, 45–64, and ≥65 years. Descriptive statistics were used to characterize the proportion of individuals with a positive PCR who met the surveillance case definition for pertussis and to describe associated signs and symptoms in individuals with a positive PCR for pertussis who did not meet the requirements for a confirmed case. Odds ratios were calculated to compare PCR positive individuals by age group, vaccination status, and signs and symptoms. Chi square tests were used to determine whether age and self-reported vaccination status were associated with meeting the surveillance case definition. The frequency and age distribution of apnea among individuals with positive PCR for pertussis were also determined. Individuals who did not meet the surveillance case definition of confirmed pertussis due to cough duration, but reported > one week of cough, one associated sign or symptom, and a positive PCR test for pertussis, were classified as suspected cases for our analysis. Suspected cases were compared to those who

met the case definition with respect to age, vaccination status, and signs or symptoms using Fisher's exact and Wilcoxon rank-sum tests.

RESULTS

Study Subjects

3090 individuals were tested for pertussis by PCR at Intermountain and 268 (8.7%) PCR assays were positive for *B. pertussis*. Proportions of PCR positivity for each age group are shown in Figure 1. PCR positivity was more common in individuals ≤ 24 compared with those > 24 years of age (208/1994 vs. 60/1096, OR 2.0, 95% CI 1.5–2.8).

UDOH Investigation of PCR Positive Cases

UDOH received reports from Intermountain facilities for 241 individuals with positive PCR test results for pertussis. Case investigation forms were completed by UDOH for 188 (78%) PCR positive individuals. Of these, 165 (88%) met the surveillance case definition requirements for confirmed pertussis.

Likelihood of Meeting Case Definition by Age and Vaccination Status

The median age of the 165 PCR positive individuals who met the surveillance case definition was 14 years vs. 13 years for the 23 individuals who did not meet the case definition ($p=NS$). There was no variation in the likelihood of meeting the case definition based on age. The proportion of immunized (i.e. $\geq$ one pertussis immunization) individuals with a positive PCR for pertussis by age ranged from a low of 13/28 (46%) for those $<$ one year old to a high of 17/18 (94%) for those 25–44 years old. Individuals $>$ four years of age with a positive PCR were more likely to give a history of receiving at least one prior pertussis immunization compared with those $\leq$ four with a positive PCR (111/117 vs. 29/54, OR 16.0, 95% CI 5.6–51.0). Even so, reported vaccination status did not significantly affect the likelihood of meeting the surveillance case definition.

Associated Signs and Symptoms Among PCR Positive Individuals Who Met or Did Not Meet the Case Definition

A comparison of PCR positive individuals who did and did not meet case definition due to insufficient cough duration but met one or more clinical criteria are summarized in Table I. Individuals younger than four years of age who met the case definition were more likely to have reported inspiratory whoop (29/47 vs. 39/113, OR 3.1, 95% CI 1.4–6.6) and post-tussive vomiting (32/48 vs. 51/117, OR 2.6, 95% CI 1.2–5.6) than older individuals who met the case definition.

Of the 23 PCR positive individuals who did not meet the surveillance case definition, the median duration of cough was 12 days (IQ range 11–13). The most common reason PCR positive individuals did not meet case definition was insufficient cough duration. 61% (14/23) of PCR positive individuals who did not meet cough duration criterion but who reported greater than one week of cough, also reported at least one other clinical sign or symptom (Table 1). The median time interval between onset of cough and PCR testing, a proxy for when the individual sought care, was significantly shorter in these 14 individuals with a shorter cough duration than in individuals who met the case definition. There was no statistical difference in the presence of these signs or symptoms between these individuals and those who met the surveillance case definition. 5/14 (36%) of these suspected cases, including four younger than one year, were unimmunized. All 14 were treated with antibiotics for pertussis.

Apnea as a Presenting Sign

Apnea was documented in 36% (60/165) of the PCR positive individuals who met the case definition. Individuals who met the case definition were more likely to have reported apnea (60/63 vs. 43/54, OR 5.1, 95% CI 1.2–29.9) than those who did not meet the case definition. Apnea associated with their pertussis illness was reported in 17/19 (89%) of PCR positive infants < one year. Infants < one year of age who met the case definition were also more likely to have reported apnea than older individuals who met the definition (15/17 vs. 45/86, OR 6.8, 95% CI 1.4–64.2).

DISCUSSION

The current pertussis surveillance case definition, which requires that a cough be present for two or more weeks, has not been revised for more than a decade. We found that this requirement means that more than 10% of individuals with a positive pertussis PCR do not meet the surveillance case definition. All of the PCR positive individuals who did not meet criteria for case confirmation were suspected to have pertussis and received treatment for pertussis. The majority (70%) had a cough > one week and at least one of the other required signs or symptoms. Including these suspected clinical cases with cough duration > one week, one or more associated criteria, and a positive PCR test would not only increase the sensitivity of the case definition, it also would improve ascertainment for surveillance and reflect the reality of current testing strategies. Based on our data we believe that expanding the case definition to include apnea as a confirmatory sign in infants may also improve the case definition.

Our study demonstrates that the current surveillance case definition may exclude many individuals with a positive PCR and symptoms consistent with pertussis. However, it is important to note that 88% of PCR positive individuals with completed case report forms did meet the surveillance case definition for confirmed pertussis. Including those with cough > one week and one or more associated symptom consistent with the case definition would result in 95% of the individuals with positive PCR for pertussis in our study group being classified as confirmed pertussis. Other investigators have reported much lower correlations between PCR positivity and pertussis symptoms. In a 2004 outbreak of respiratory illness in Tennessee only 5% of those with a positive PCR for pertussis had a cough with a duration of more than two weeks. In a 2006 New Hampshire outbreak, retrospective interviews documented that 21% of health care personnel with suspected pertussis did not report a cough of any duration, and, among those who reported cough, 35% did not report any other classic pertussis symptom. In a 2006 Massachusetts outbreak of respiratory illness, 92% of those with a positive PCR had none of the classic pertussis symptoms, and there was poor agreement with respect to PCR results between laboratories.¹⁷ Since there are no standardized PCR assays for pertussis and no PCR product has been approved by the FDA, assay procedures and sensitivity and specificity may vary greatly between laboratories. We consider these false positive results to emphasize the need for stringent quality control measures in PCR testing to ensure accurate laboratory diagnosis and the importance of limiting testing to symptomatic patients.

Modifying the current definition to include individuals with more than one week of cough (rather than two weeks), a positive PCR, and one or more of the other criteria, would increase the number of confirmed pertussis cases. Since the patient or their caregiver determines the timing for seeking medical care and the current surveillance case definition requires two weeks of cough in the presence of a positive PCR, a significant proportion of clinically likely and laboratory confirmed cases may be excluded by the current definition. Excluded cases in our study had a shorter time interval between onset of signs or symptoms and seeking of medical treatment. Consequently these individuals had a cough with a shorter

duration at the time of interview but they were just as likely to have one or more of the associated signs or symptoms as individuals who did meet the case definition. It is not known whether a longer cough interval would have been found if the individuals were interviewed a second time. However, a second interview would place significant burden on public health providers.

In addition to the problems related to cough duration, apnea, which is known to be commonly present in infants with pertussis in the absence of cough,¹⁸ is not included in the surveillance case definition. In our study 89% of PCR positive individuals younger than one year of age had associated apnea and infants who met the case definition were more likely to have reported apnea than older individuals who met the definition. A previous study reported that apnea was a presenting sign in 52 percent in children < one year of age who were subsequently hospitalized for pertussis.¹⁹ Another study demonstrated apnea with or without paroxysmal cough in 63% of infants diagnosed with pertussis who later required intensive care.²⁰ We suggest that the case definition needs to be revised to include apnea as a sign for infants. This sign appears to be equivalent in importance to cough duration. Failing to include apnea may exclude individuals, particularly infants with pertussis.

Excluding true cases of pertussis from the surveillance system may be problematic for several reasons. First, it results in an underestimation of the incidence of disease. Second, the timing of care seeking behavior, increased use of rapid testing, and improved reporting systems may influence exclusion. Each of these issues could result in earlier identification and treatment of pertussis and investigation by the health department before the required two weeks have elapsed. Finally, health care providers, families, and schools may be confused by the public health exclusion of cases from surveillance case counts after a clinician has obtained laboratory confirmation, treated a patient, and the health department has implemented control measures. The exclusion is not consistent with the public health effort and may result in decreased physician testing, reporting, delayed treatment, and inadequate public health prevention measures.

Our study has several limitations. Since clinical data collected during case investigation is largely based on self-report, there may be inaccuracies in the precision of timing or presence of some signs or symptoms leading to potential misclassification. Investigatory practices vary by local health department, and missing data may reflect the variability of resources allocated to data collection. False positive PCR results due to cross-reactivity with *B. holmesii* are another potential concern. Although false positive results for *B. pertussis* may occur in samples containing *B. holmesii* DNA, several large PCR studies have found the incidence of *B. holmesii* to be extremely low or undetectable.^{21,22} Finally, there is also uncertainty regarding the duration of positivity of a PCR test following recovery from pertussis. This concern further supports the incorporation of clinically relevant signs or symptoms along with PCR results into the case definition.

CONCLUSIONS

Decreasing cough duration from $\geq$ two weeks to > one week would result in 95% of those with positive PCR meeting confirmation criteria for pertussis. Apnea should be considered an additional sign for pertussis confirmation in infants.

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REFERENCES

- Centers for Disease Control and Prevention (CDC). Summary of notifiable diseases--United States, 2006. MMWR Morb Mortal Wkly Rep. 2008; 55(53):1-92. [PubMed: 18354375]
- Wharton, M.; Strebel, PM. VPD Surveillance Manual. Atlanta, GA: Centers for Disease Control and Prevention; 1997. Chapter 20: National Surveillance of Vaccine-Preventable Diseases; p. 1-8.
- Council of State and Territorial Epidemiologists Web site. CSTE Position Statement 1997-ID-9. [Accessed November 13, 2008] Public Health Surveillance, Control, and Prevention of Pertussis. <http://www.cste.org/ps/1997/1997-id-09.htm>.
- Council of State and Territorial Epidemiologists Web site. CSTE Position Statement 11 f. [Accessed November 13, 2008] Pertussis. <http://www.cste.org/ps/pssearch/1994/1994-all.htm>.
- National Notifiable Diseases Surveillance System Web site. [Accessed October 30, 2008] Pertussis (Bordetella pertussis) (Whooping Cough). 1997. Case Definition, http://www.cdc.gov/ncphi/diss/nndss/casedef/pertussis_current.htm.
- Atkinson, W.; Hamborsky, J.; McIntyre, L.; Wolfe, S. Epidemiology and prevention of vaccine-preventable diseases. 10th ed.. Washington DC: Public Health Foundation; 2008.
- Gerstman, BB. Epidemiology kept simple: an introduction to traditional and modern epidemiology. 2nd ed.. Hoboken, NJ: Wiley; 2003.
- Tan T, Trindade E, Skowronski D. Epidemiology of pertussis. Pediatr Infect Dis J. 2005; 24 Suppl 5:S10-S18. [PubMed: 15876918]
- Baptista PN, Magalhães VS, Rodrigues LC. Children with pertussis inform the investigation of other pertussis cases among contacts. BMC Pediatr. 2007; 7:21. [PubMed: 17518997]
- Centers for Disease Control and Prevention (CDC). Notice to Readers: Final 2006 Reports of Nationally Notifiable Infectious Diseases. MMWR. 2007; 56(33):851-863.
- Centers for Disease Control and Prevention (CDC). Notice to Readers: Final 2007 Reports of Nationally Notifiable Infectious Diseases. MMWR. 2008; 57(33):901-913.
- Utah Department of Health Web site. [Accessed November 9, 2008] Trends in Pertussis Activity, Utah, 1995. 2005. health.utah.gov/epi/anrpt/anrpt05/pert_ut_9505_final.pdf.
- De Donno A, Quattrocchi M, Ansaldi F, Campa A, Rollo MC, Gabutti G. Direct detection of Bordetella pertussis and Bordetella parapertussis: comparison of polymerase chain reaction and culture. J Int Med Res. 2006; 34(4):367-373. [PubMed: 16989492]
- Templeton KE, Scheltinga SA, van der Zee A, et al. Evaluation of real-time PCR for detection of and discrimination between Bordetella pertussis, Bordetella parapertussis, and Bordetella holmesii for clinical diagnosis. J Clin Microbiol. 2003; 41(9):4121-4126. [PubMed: 12958235]
- Schmidt-Schlöpfer G, Liese JG, Porter F, Stojanov S, Just M, Belohradsky BH. Polymerase chain reaction (PCR) compared with conventional identification in culture for detection of Bordetella pertussis in 7153 children. Clin Microbiol Infect. 1997; 3(4):462-467. [PubMed: 11864157]
- Biosystems, A. [user bulletin] ABI PRISM 7000 Sequence Detection System and Applied Biosystems 7500 Real-Time PCR System. Foster City, CA: Applied Biosystems; 2007.
- Centers for Disease Control and Prevention (CDC). 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. [PubMed: 17717512]
- Feigin, RD.; Cherry, J.; Demmler, G.; Kaplan, S. Textbook of Pediatric Infectious Diseases. 5th ed.. Philadelphia, PA: Saunders; 2004.
- Bhatt P, Halasa N. Increasing rates of infants hospitalized with pertussis. Tenn Med. 2007; 100(5): 37-39. 42. [PubMed: 17542362]
- Namachivayam P, Shimizu K, Butt W. Pertussis: severe clinical presentation in pediatric intensive care and its relation to outcome. Pediatr Crit Care Med. 2007; 8(3):207-211. [PubMed: 17417115]
- Knorr L, Fox JD, Tilley PA, Ahmed-Bentley J. Evaluation of real-time PCR for diagnosis of Bordetella pertussis infection. BMC Infect Dis. 2006; 6:62. [PubMed: 16556317]

22. Antila M, He Q, de Jong C, et al. *Bordetella holmesii* DNA is not detected in nasopharyngeal swabs from Finnish and Dutch patients with suspected pertussis. *J Med Microbiol.* 2006; 55:1043–1051. [PubMed: 16849724]

Figure 1.
Pertussis PCR Test Results by Age Group, Intermountain Healthcare, Utah, 11/2004–
06/2006

Table 1

Comparison of PCR Positive Individuals by Case Definition Status

	PCR Positive and Met Case Definition (n= 165)	PCR Positive and Did Not Meet Case Definition Due to Cough Duration (n=14)	p value
Median Duration of Cough in Days (IQ Range)	28 (20–40)	11.5 (11–12)	<0.001
Median Time Between Cough Onset and PCR Testing in Days (IQ Range)	14 (9–20)	7 (5–8)	<0.001
Median Age in Years (IQ Range)	14 (4–18)	10.5 (0.4–17)	0.458
Paroxysms of Coughing (%)	98% (161/164)	100% (14/14)	1.0
Whoop (%)	43% (68/160)	50% (7/14)	0.588
Post-tussive Vomiting (%)	50% (83/165)	50% (7/14)	1.0