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Evaluating the role of cough duration in the pertussis case definition among Michigan cases, 2000–2010

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ABSTRACT

Impressive reductions in pertussis have been achieved in the U.S. during the 20th century through childhood vaccination. Over the past two decades, increasing pertussis incidence has highlighted the need for accurate and timely reporting of cases to improve prevention and control efforts. We assessed components of the pertussis case definition, comparing use of clinical characteristics and laboratory results and their effects on internal validity, including an examination of the 2014 infant case definition. All reported pertussis cases in Michigan during 2000–2010 with data on cough length ($N = 3310$) were analyzed using multivariate statistics to internally validate reported cases, and calculate odds of meeting the clinical case definition, including a cough of at least 14 days. Cough duration of reported cases averaged 32 days and was longer with greater time interval between cough onset and initial presentation to a physician. Only about half of reported cases had positive laboratory results. Among cases seeking medical evaluation prior to meeting the cough duration required to fulfill the clinical case definition, the presence of positive lab results doubled the odds that the cough duration was not met compared to cases without a positive lab test. Clinical characteristics of pertussis are frequently ignored in applying the case classification. Relying solely on laboratory confirmation and disregarding clinical characteristics results in undiagnosed pertussis cases among those who are vaccinated, among adults, and among anyone who delays seeking care. This may prevent use of appropriate prevention and prophylaxis in contacts.

1. Introduction

Pertussis is a common and potentially serious childhood respiratory illness caused by the bacterium *Bordetella pertussis*. It is clinically characterized by a prolonged cough sometimes accompanied by an inspiratory whoop from which the name "whooping cough" is derived. Infants typically present with more severe illness sometimes resulting in hospitalization, and accounting for 53% of the 160,700 global pertussis-associated deaths. (Yeung et al., 2017) The severity of illness can be mitigated with the use of antibiotics (Carlsson et al., 2015) and prevented through age-appropriate immunization with a four-dose primary series beginning at two months of age, followed by booster doses as the child ages (McNamara et al., 2017; Robinson, 2016; Folkhälsomyndigheten, 2018)

As a nationally notifiable disease, reporting of all confirmed and probable pertussis cases to state public health authorities is legally required. The U.S. Centers for Disease Control and Prevention (CDC) pertussis case definition is complex, as a case can be confirmed through a variety of clinical, laboratory, and epidemiological criteria used in different combinations, and use of these criteria can vary in infants versus children, adolescents and adults (Fig. 1). Currently, a cough lasting 14 days is required for cases to be reported, with two notable exceptions that are reportable with any cough duration: 1) anyone with a positive bacterial culture, or 2) infants presenting with a cough of any duration, plus a cough attribute (i.e. paroxysms, whoop, post-tussive vomiting, or apnea), and either a positive PCR test or an epidemiologic link to another lab-confirmed case (CDC, 2014). While nuances within the case definitions are intended to increase sensitivity, the very complexity of that definition can lead to misdiagnosis, and a decrease in reliability of reported cases since there is likely to be great variation across reporting sources.

In clinical practice, a persistent cough is central to suspecting and diagnosing pertussis (Ebell et al., 2017). Cough is unusually prolonged with pertussis, and can often linger for weeks or even months after

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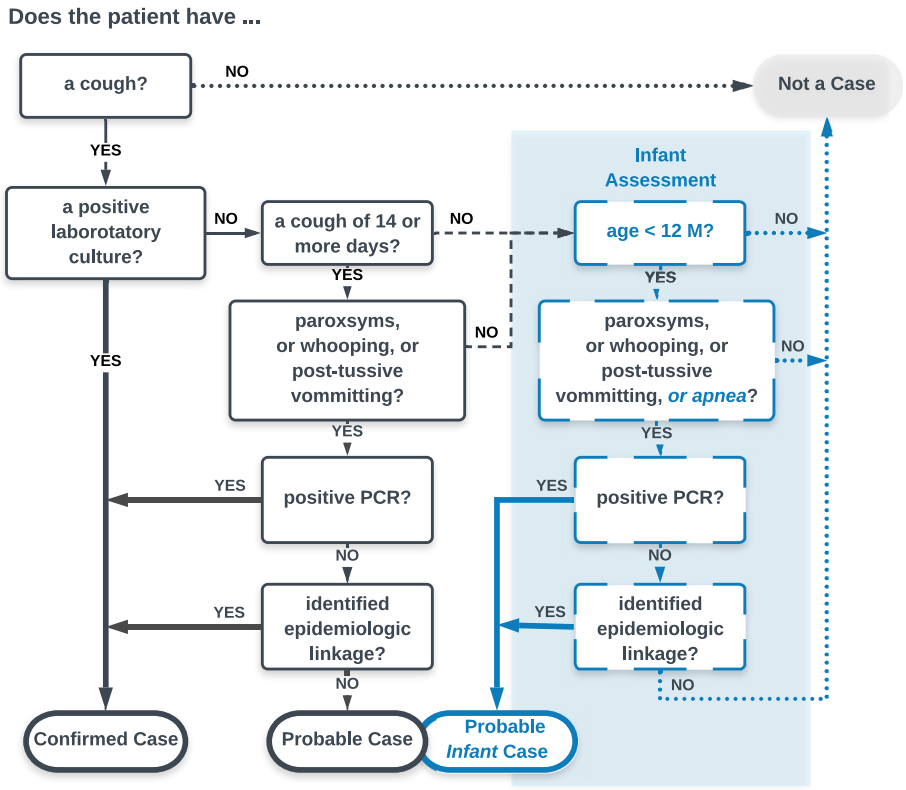

Fig. 1. Flowchart of U.S. CDC pertussis case classification-based on reporting criteria for public health surveillance. (CDC, 2014).

initial infection (Bortolussi et al., 1995; Brennan et al., 2000; Jõgi et al., 2018). The current case definition for probable pertussis is based on clinical criteria, and was established in 1990, when the CDC shortened the minimum cough duration to 14 days (from 21 days), accompanied by the presence of at least one other cough attribute (i.e. paroxysms, whoop, or post-tussive vomiting) (CDC, 1997). Probable clinical cases are considered to become confirmed cases if they meet either laboratory or epidemiological criteria including: 1) laboratory testing (positive culture or polymerase chain reaction (PCR) evidence of *B. pertussis*), or 2) documented contact with another laboratory-confirmed case (CDC, 1997; CDC, 2014) (Fig. 1). Both probable and confirmed pertussis cases are reportable to state health authorities, although in one study, only 19% of urgent care providers were aware that clinically diagnosed pertussis cases were reportable (Staes et al., 2009).

While a protracted (≥14-day) cough associated with specific cough attributes leads to high clinical suspicion of a *B. pertussis* infection, that combination nonetheless lacks specificity (Ebell et al., 2017; Jõgi et al., 2018); therefore, clinicians often use laboratory testing to confirm the diagnosis. The sensitivity of *B. pertussis* molecular testing depends on the patient's age, when the sample was collected, antibiotics taken, and vaccination status. Culture-based testing has recently declined due to the time required for results and lower sensitivity of this approach, which identifies only 8–40% of PCR-positive samples (Bowden et al., 2014; DeVincenzo et al., 2013; Faulkner et al., 2016; Jõgi et al., 2018; Folkhälsomyndigheten, 2018; van der Zee et al., 2015). PCR testing was first designated by the CDC as a confirmatory test for pertussis in 1997, but only among cases meeting the probable case definition (CDC, 1997). The use of PCR testing for pertussis has increased substantially since then (Faulkner et al., 2016). Shakib et al. evaluated the cough duration criterion among PCR-positive cases who also had a cough attribute (Shakib et al., 2009). Their study of 268 PCR-positive suspected cases from Utah during a 20-month period found that 12% of these cases did not meet the probable case definition with a cough of at least 14 days duration, although they fulfilled the laboratory criterion.

In this study, we analyzed all pertussis cases reported in the state of Michigan as part of routine public health surveillance during 2000–2010. We evaluated the use of the pertussis case definition's cough criterion for reported cases. Specifically, we investigated whether there were systematic differences between reported cases that met the 14-day criterion and those that did not, to determine which, if any, of the case definition criteria were prone to misinterpretation and subsequent misidentification of cases.

2. Materials and methods

2.1. Study population

Cases of pertussis reported to the Michigan Department of Health and Human Services (MDHHS) during an 11-year period from 1 January 2000 through 31 December 2010, as part of the State's routine surveillance for nationally notifiable diseases, were analyzed. During the study period, two different reporting systems were used to transmit information on notifiable diseases from clinical providers, laboratories, hospitals, and local health departments (LHDs) to the MDHHS. A DOS-based reporting system that operated from 1992 to 2004 permitted weekly transmittal of notifiable diseases records from LHDs to the MDHHS. In June 2004, the web-based Michigan Disease Surveillance System (MDSS) was launched. In addition to reports from LHDs, the MDSS also integrates data from primary care providers, hospitals and electronic laboratory reports. The new MDSS enhanced Michigan's public health surveillance capacity by increasing timeliness and completeness of case reporting in a manner comparable to that seen in other states implementing similar web-based reporting systems (Effler et al., 1999; Gamache et al., 2012; Wurtz and Cameron, 2005).

Providers reporting a pertussis case must complete the required data fields on a standardized MDHHS pertussis case report form (based on the CDC reporting form found at: http://www.cdc.gov/vaccines/pubs/surv-manual/appx/appendix11-2-pertussis-wrsht.pdf), which includes

questions about case demographics, contact details and clinical case information, including cough length, treatment and diagnostic testing. Healthcare providers and LHDs using the MDSS can review and/or update their case reports when additional information becomes available.

2.2. Data preparation

In Michigan, most non-outbreak pertussis cases are reported through passive surveillance (i.e. without active case-finding or active solicitation of reports by public health workers), and missing values are common. Therefore, some variables were re-coded to minimize the missing data (described below). Dichotomous variables were re-coded so that a 'Yes' response was retained, but a 'No' response was treated as either a reported absence of the clinical characteristic, or as missing from the report. This is the most conservative approach to retain the majority of the data for dichotomous variables. Vaccination status only indicated whether a record of DTP/DT vaccination was available; therefore "No," "Unknown," and missing were all interpreted as records not found. Records associated with older ages tended to be "not found" due to missing documentation, which may not represent the actual vaccination status. The initial healthcare visit date was based on the earliest reported date of antibiotic prescription, as this was the most complete variable. Because only two cases were reported to not be taking antibiotics, our analysis represented findings from a population that almost always received antibiotics on their first medical visit, which is consistent with pertussis reporting from other surveillance systems (Baggett et al., 2007; McNamara et al., 2017).

Cases were categorized as probable or confirmed according to the CDC case classification. Infants who could not be definitely categorized as confirmed or probable were retrospectively classified according to the 2014 Infant Case Definition, which was not available at the time they were reported (i.e. during the time period of this study).

2.3. Statistical analysis

Cases were divided into two groups based on whether the patient sought healthcare during the first 13 days of coughing, or on the 14th or later days of coughing. The second group, which met the clinical case definition for 14-day cough length at their first medical visit, was not included in analyses in the context of whether cough length was sufficient to have met the case definition. However, both groups were compared using paired *t*-tests with the Satterthwaite method of unequal variances to determine whether descriptive variables differed significantly between the two groups. Case frequencies were classified by clinical combinations and case-classification before excluding cases who met the cough length criterion on their initial visit.

Bivariate logistic regression predicting the likelihood of failing to meet the cough criterion was run for all case classification variables, and also for vaccination status, county of residence, age, ethnicity, and macrolide prescription. The modeled outcome was based on the reported cough duration value. Correlations between numeric variables were also tested. Highly correlated and conceptually related variables were assessed for collinearity using the variance inflation factor. Multivariate logistic regression models were constructed using a two-stage backward model selection. The initial stage included all significant, non-collinear, individual predictors, which were removed in reverse order of significance. The final decision on inclusion of a predictor was based on model fit criteria as quantified by the lowest AIC value. A sensitivity analysis was conducted for an alternative outcome measure, namely the best estimated duration of cough that was calculated from the data, and this slightly increased the sample size.

All analyses were conducted using SAS version 9.3 (Cary, NC). Data acquisition and analysis was approved by the Institutional Review Boards of the University of Michigan and the Michigan Department of Health and Human Services.

3. Results

The original data set contained 4800 individual patient records reported as either probable or confirmed pertussis cases. Six cases with laboratory results indicating *Bordetella parapertussis* infection were excluded from analysis. Other cases were excluded for lack of evidence of cough ($N = 206$) or missing an initial healthcare visit date ($N = 519$). Additional exclusions involved 28 cases with missing patient age, 33 cases lacking antibiotic information, and 698 cases without cough duration information, leaving a total of 3310 cases (69.0%) included in the study population. The regression analysis was specifically based on the 1884 cases who sought medical attention before 14 days of cough had elapsed, although all 3310 cases are characterized (Tables 2-4).

3.1. Characteristics of cases seeking healthcare before and after 14 days of cough

Among 3310 cases, the median cough duration was 26 days (interquartile range (IQR): 17–40 days). The time between cough onset and antibiotic prescription for school-aged children (5–19 years old) and adults averaged 16 (range: −19-151) and 18 (range: −24-362) days, respectively. Both were longer intervals than for children under five years of age, whose mean cough-to-prescription time was 14 days (range −28-104 days).

Tables 1 and 2 further describe the characteristics of the reported pertussis cases and the timing of key medical events following cough onset. At least one of the three cough attributes (i.e. paroxysms, inspiratory whoop, post-tussive vomiting), was reported for most (89.5%) cases (Table 1). Among those who had no reported cough attribute, 44.0% were school-aged while the remainder were nearly evenly divided between younger children (29%) and adults (27%). The reported clinical course of disease was shorter among cases who visited their healthcare provider before, versus after, 14 days of cough with averages of 25.8 and 42.6 days, respectively (Table 2). Other characteristics that differed significantly between those who received medical attention before vs. after 14 days included: lower frequency of paroxysms and post-tussive vomiting among the < 14-day cases, but higher proportions of PCR positives and of epidemiologically linked cases among those with the ≥14 day of cough.

3.2. Characteristics used to define cases

Case confirmation was based on clinical symptoms and other qualifying criteria for the case definition (Table 3). Among the 2755 (83%) cases who met the clinical case definition, 326 (10%) could be confirmed by culture, 1524 (46%) by PCR and 466 (17%) by epidemiologic linkage. The remaining 1007 cases meeting the clinical case definition could not be confirmed, because they did not have a laboratory result or any report of an epidemiological link. Fifty-seven (17%) culture positive cases did not meet the clinical case definition, compared to 328 (22%) of those PCR positive, and 171 (27%) of those reporting an epidemiological link (Table 2). Most of the infants met a confirmed or probable case definition, 511/ 590 (87%); of the 79 who did not, 54 infants (68%) could be classified as probable cases and 5 (6%) new infants were confirmed under the new 2014 pertussis infant case definition (CDC, 2014). Overall, 84 (3%) of all cases could not be classified as probable or confirmed cases according to the information provided.

Multivariable logistic regression of the 1884 study cases who visited a physician before meeting the cough criteria (i.e. prior to 14 days cough duration), revealed that the presence of any cough criterion significantly decreased the odds of reporting less than fourteen days of cough (Table 4). Conversely, a patient testing positive for pertussis by culture, PCR, or epi-link increased 1.4 to 2.0 times the odds that the final reported cough duration would not fulfill the length required by the clinical case definition (Table 4). The sensitivity analysis using the calculated cough duration produced comparable results (data not

Table 1
Descriptive statistics for 3310 pertussis cases reported by cough duration relative to time of medical evaluation among Michigan residents, 2000–2010.

Dichotomous variables	Before [a] 14 days of cough $N = 1884$		On or after [a] 14 days of cough $N = 1426$		Satterth-waite *t*-test
	%	(95% CI)	%	(95% CI)	*P* value
Male gender	42.7	(40.4–44.9)	43.9	(41.3–46.4)	0.50
Macrolide antibiotic given	69.5	(67.4–71.6)	70.9	(68.5–73.3)	0.38
Coughing at final interview [b]	82.6	(80.9–84.4)	82.3	(80.3–84.3)	0.98
Any cough attribute	89.5	(88.2–90.9)	92.5	(91.1–93.9)	< **0.01**
Whooping	37.5	(35.3–39.7)	36.7	(34.2–39.2)	0.64
Paroxysms	83.9	(82.2–85.5)	86.8	(85.1–88.6)	**0.02**
Post-tussive vomiting	49.2	(46.9–51.5)	54.3	(51.7–56.9)	< **0.01**
Apnea	35.1	(33.0–37.3)	34.8	(32.3–37.3)	0.83
Any lab test positive	59.7	(57.4–61.9)	49.2	(46.6–51.8)	< **0.01**
Culture positive	10.3	(8.9–11.7)	9.3	(7.8–10.8)	0.32
PCR positive	50.1	(47.9–52.4)	40.7	(38.1–43.2)	< **0.01**
Epidemiologic linkage	20.4	(18.6–22.2)	17.7	(15.8–19.7)	**0.05**
Outbreak associated	17.2	(15.5–18.9)	20.5	(18.4–22.6)	**0.02**
Vaccination record	59.5	(57.3–61.7)	59.8	(57.3–62.4)	0.85

[a] Cases are grouped into those who first visited a medical provider before 14 days of cough, and those seen on or after 14 days of coughing. Symptoms, laboratory test results, treatment and epidemiological characteristics were reported on or after the first healthcare visit.
[b] The final interview is a variable in the surveillance report giving the status of the case the last time the case was seen for this illness, it does not specify the number of visits.

Table 2
Descriptive Mean Statistics of 3310 pertussis cases reported by cough duration relative to time of medical evaluation among Michigan residents, 2000–2010.

Continuous variables	Before[a] 14 days of cough N = 1884		On or after [a] 14 days of cough N = 1426		Satterth-waite t-test
	Mean	(95% CI)	Mean	(95% CI)	*P*-value
Age in years	18.3	(17.3–19.2)	18.7	(17.6–19.7)	0.58
Days to 1st antibiotic [b]	6.3	(6.1–6.5)	28.7	(27.5–30.0)	< 0.01
Days to PCR[b]	9.2	(8.7–9.6)	25.3	(24.0–26.6)	< 0.01
Days to diagnosis [b]	13.0	(12.3–13.7)	30.7	(29.0–32.4)	< 0.01
Days of cough	25.8	(25.0–26.6)	42.6	(41.1–44.1)	< 0.01
Cough ended	24.2	(22.2–26.2)	45.4	(41.9–48.9)	< 0.01
Cough ongoing	26.1	(25.2–27.0)	42.0	(40.4–43.7)	< 0.0

[a] Cases are grouped into those who first visited a medical provider before 14 days of cough, and those seen on or after 14 days of coughing. Symptoms, laboratory test results, treatment and epidemiological characteristics were reported on or after the first healthcare visit.
[b] All time intervals are from the date of cough onset to the date specified.

Table 4
Odds of reporting < 14 days of cough among pertussis cases medically evaluated prior to meeting cough case definition criteria, 2000–2010. (N = 1884).

Parameter	Odds ratio	95% CI
Age group		
Child (0–4 yrs)	Ref	
School-aged (5–19 yrs)	0.443	(0.324–0.606)
Adult (20+ yrs)	0.430	(0.310–0.623)
Post-tussive vomiting	0.575	(0.432–0.765)
Paroxysms	0.392	(0.280–0.532)
Whooping	0.715	(0.535–0.956)
Cough cessation	0.724	(0.527–0.995)
Culture positive	2.019	(1.301–3.132)
PCR positive	2.087	(1.557–2.798)
Epidemiologic linkage	1.404	(1.028–1.917)
Antibiotic		
Macrolides	Ref	
Beta-lactams	0.328	(0.179–0.601)
Other/unspecified	0.816	(0.456–1.463)

Note: For all variables without a designated reference category, the reference group is absence of the variable.

Table 3
Prevalence of clinical symptoms, epidemiologic and laboratory case definition criteria among 3310 pertussis cases, 2000–2010.

Symptoms [b]	Total		Confirmed [a]		Culture		PCR		Epi-link		Clinical		Other	
	N	% [c]	N	%	N	%	N	%	N	%	N	%	N	%
ALL	3310		1810	54.7	326	9.8	1524	46.0	637	19.2	1012	30.6	84	2.5
C +1	2755	83.2	1748	63.4	269	9.8	1196	43.4	466	16.9	1007	36.6		
C _	201	6.1	14	7.0	14	7.0	106	52.7	82	40.8			35	17.4
_ +1	199	6.0	36	18.1	36	18.1	124	62.3	47	23.6			21	10.6
_ _	76	2.3	7	9.2	7	9.2	34	44.7	35	46.1			17	22.4
C _ (i)	17	0.5	5[d]	29.4			13	76.5	2	11.8	5[d]	29.4	3	17.6
_ + 1(i)	55	1.7					47	85.5	4	7.3			5	9.1
_ _ (i)	7	0.2					4	57.1	1	14.3			3	42.9

[a] Columns are not mutually exclusive categories; records may appear multiple times.
[b] Symptoms are summarized in three parts. Firstly, if a cough was documented of > 14 days duration (C). Secondly, if one of the cough characteristics (whoop, paroxysms, post-tussive vomiting) was present (+1). Finally, infants (i), not classified as confirmed or probable were re-classified according to the 2014 infant case definition.
[c] Total percentage is calculated as the proportion of the column.
[d] These infants reported apnea, which is only part of the infant classification.

shown). Variables associated with meeting the clinical cough length criterion included: age of five years or older, having a coincident cough attribute, the documented end of cough, and initial treatment with beta-lactam antibiotics (not the recommended macrolides: azithromycin, erythromycin or clarithromycin) (Table 4). Each of the three confirmatory criteria, (i.e. positive lab culture, positive PCR, or epidemiologic linkage) were associated with a greater likelihood that the 14-day cough during criterion was not met.

4. Discussion

While pertussis incidence has been declining in the U.S. since the mid-20th century, the past three decades have been characterized by increased incidence with cyclic and large epidemics (Kilgore et al., 2016; Winter et al., 2014). Pertussis incidence among both adolescents and adults has increased, despite diagnostic challenges of atypical or mild symptoms and delayed healthcare seeking behaviors (Goodenough et al., 2016; Kilgore et al., 2016). Delay in treatment increases the risk of transmission and further fuels the large-scale outbreaks (Goodenough et al., 2016; Kenyon et al., 2014; Skoff et al., 2012; Winter et al., 2014). In light of the changing epidemiology, and the risk for greater spread with delayed diagnosis, clinical characteristics continue to be a relevant, if frequently ignored, diagnostic criteria for clinicians in the identification of pertussis, especially among adults and vaccinated individuals (Domínguez et al., 2017; Goodenough et al., 2016).

Our study demonstrated that a positive laboratory result by either culture or PCR, doubled the odds of failing the 14-day cough criterion. Prioritizing laboratory and epidemiological criteria over clinical criteria resulted in cases seeking medical care before 14 days, thereby failing the probable case definition. For all probable cases over one year of age, the presence of a confirmatory criterion substantiates, but does *not* eliminate, the need to meet the clinical case definition.

Studies have shown that a cough length of 14 or more days is the most sensitive of the clinical characteristics, although cough attributes (e.g. paroxysms, post-tussive vomiting) have higher specificity (Domínguez et al., 2017; Ebell et al., 2017; Jõgi et al., 2018; Moore et al., 2017). The shifting age epidemiology of pertussis cases, with longer time to treatment (Goodenough et al., 2016), makes it less likely that cases will be laboratory positive, and requires broader utilization of the clinical case definition, thereby improving reporting of probable pertussis cases to better characterize population-level susceptibility.

Our study may have been limited by incomplete reporting of the case definition criteria, and case investigations which were closed before the cough resolved. Among reported cases of pertussis, we found that 12% of those who were PCR positive cases did not have a cough lasting ≥14 days, which are results similar to the those of Shakib et al. (Shakib et al., 2009). We are unable to determine whether this was due to incomplete follow-up or early cessation of cough, but it is unlikely to be due to receipt of antibiotics since antibiotics do not generally shorten cough duration (Carlsson et al., 2015; Halperin et al., 1999; Knapp et al., 2016; Folkhälsomyndigheten, 2018). To address this issue, we used conservative statistical methods, substituting a negative response for missing bivariate data. It is also reassuring that our cough attributes had similar frequencies to those reported in other surveillance studies (Bortolussi et al., 1995; Domínguez et al., 2017; Goodenough et al., 2016; Jõgi et al., 2018; Kilgore et al., 2016; McNamara et al., 2017; Shakib et al., 2009).

Infant cases are known to be under-reported and challenging to confirm (Solano et al., 2016). Therefore, by investigating whether the 2014 probable *infant* case definition (CDC, 2014) classification would increase the reportable infants, we found an additional 8% of infants captured by the new classification. This value likely underrepresents the impact of the new classification, as infants in our study were reported according to the prior guidelines.

Because ~80% of cases in our study were "still coughing" during the final healthcare visit, our analysis was necessarily based on incomplete cough duration data. Of two studies that followed pertussis cases to cough cessation, the mean cough duration was 60 days (Bortolussi et al., 1995) and 104 days (Jõgi et al., 2018), which is more than twice that of our study. Although follow-up frequently ended before cough cessation, the Michigan cases were followed longer than the peak infectious period (mean infection interval 23 days (Kilgore et al., 2016)), which is sufficient for diagnosis, treatment and follow-up of possible contacts.

Our findings suggest a systematic overreliance on confirmatory laboratory criteria to classify and report pertussis cases, with incomplete reporting of supporting clinical information. This has been observed in other studies as well (Shakib et al., 2009; Solano et al., 2016; Staes et al., 2009). While laboratory testing is an essential part of diagnostic confirmation, it has limitations when conducted following antibiotic administration, in adult patients, and after 14 days of coughing. Clinical characteristics such as cough length are critical diagnostic information to establish a diagnosis, especially where healthcare access is limited due to geography, resources or other reasons. Sensitive surveillance through accurate and early detection are key for a timely response given the increasing incidence of pertussis and the return of cyclic epidemics in the United States. Insuring that healthcare providers properly use the clinical criteria in pertussis surveillance, in addition to the laboratory and epidemiologic criteria not only enhances reporting of valid cases, it is essential to identifying and reaching socially vulnerable populations through targeted control efforts.

ICMJE statement

All authors contributed significantly to this work. Data access was facilitated by MLB, through the Michigan Department of Health and Human Services. Study design was conducted by JKK MLB and MLW. Analysis was done by JKK and guided by SM. The manuscript was written and revised by JKK, MLB, and MLW.

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Ethical approval

This study was approved by the Institutions Reviews Board of the University of Michigan, and the Michigan Department of Health and Human Services, as secondary analysis of de-identified data collected for non-research purposes.

Declaration of competing interest

The authors declare no potential conflicts of interest.

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