Practice of Epidemiology

Using a Bayesian Latent Class Model to Evaluate the Utility of Investigating Persons with Negative Polymerase Chain Reaction Results for Pertussis

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Pertussis remains difficult to control. Imperfect sensitivity of diagnostic tests and lack of specific guidance regarding interpretation of negative test results among patients with compatible symptoms may contribute to its spread. In this study, we examined whether additional pertussis cases could be identified if persons with negative pertussis test results were routinely investigated. We conducted interviews among 250 subjects aged ≤18 years with pertussis polymerase chain reaction (PCR) results reported from 2 reference laboratories in Wisconsin during July–September 2010 to determine whether their illnesses met the Centers for Disease Control and Prevention’s clinical case definition (CCD) for pertussis. PCR validity measures were calculated using the CCD as the standard for pertussis disease. Two Bayesian latent class models were used to adjust the validity measures for pertussis detectable by 1) culture alone and 2) culture and/or more sensitive measures such as serology. Among 190 PCR-negative subjects, 54 (28%) had illnesses meeting the CCD. In adjusted analyses, PCR sensitivity and the negative predictive value were 1) 94% and 99% and 2) 43% and 87% in the 2 types of models, respectively. The models suggested that public health follow-up of reported pertussis patients with PCR-negative results leads to the detection of more true pertussis cases than follow-up of PCR-positive persons alone. The results also suggest a need for a more specific pertussis CCD.

Bayesian analysis; Bordetella pertussis; pertussis; polymerase chain reaction; predictive value of tests; public health surveillance; sensitivity; whooping cough

Abbreviations: BCI, Bayesian credible interval; CCD, clinical case definition; CDC, Centers for Disease Control and Prevention; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value; WIP, Wisconsin Immunization Program.

Pertussis remains one of the most common vaccine-preventable diseases in the developed world, with infants being at greatest risk of severe complications (1). While widespread immunization is the most effective means of prevention, accurate reporting is vital to invoking control measures and limiting spread when pertussis occurs in a community.

Clinical identification of pertussis is complicated by its variable presentation. “Classic” pertussis, characterized by weeks of paroxysms, posttussive vomiting, and whoop, is most common among unvaccinated children, but milder pertussis with a shorter, less severe cough has been recognized (1–3). Laboratory testing is important to confirm Bordetella pertussis infection. Polymerase chain reaction (PCR) is now commonly requested by health-care providers suspecting pertussis because it is more sensitive than culture and results are rapidly available (4). Results of PCR testing require interpretation in conjunction with signs, symptoms, and available epidemiologic information (5), because negative results can occur despite the presence of infection. Differences in nasopharyngeal bacterial load due to age, testing delay, vaccination history, and deficiencies in specimen collection and processing can affect the ability of PCR to detect B. pertussis (1, 6–10).

With no Food and Drug Administration-approved PCR assay, testing methods and validity measures vary. The
sensitivity of pertussis PCR testing is most commonly calculated using culture as the gold standard. While highly specific, *B. pertussis* culture has low sensitivity (11, 12). Thus, calculations of PCR sensitivity using culture as the gold standard may overestimate the ability of PCR to detect all pertussis infections. Evidence from serological testing demonstrates that pertussis culture and PCR positivity correlate with greater symptom severity (9), suggesting that culture and PCR might be less reliable among patients with milder symptoms.

Bayesian latent class modeling, which is used to estimate diagnostic test parameters in the absence of a gold standard (13), can be used to incorporate such evidence into estimates of validity measures for PCR. With this approach, true disease status is modeled as an unobserved “latent” class and crude measures of validity can be adjusted on the basis of published information. A single gold standard test is not assumed; each test is regarded as imperfect in diagnosing true pertussis disease status. Pertussis testing modalities have previously been evaluated using latent class modeling (14), but to our knowledge this method has never been applied to improving routine pertussis surveillance.

During a 2004 statewide pertussis outbreak in Wisconsin, 2 laboratories (laboratory A and laboratory B) conducting the majority of pertussis testing in Wisconsin began reporting both negative and positive pertussis test results to the Wisconsin Immunization Program (WIP). Laboratories A and B continue to report negative pertussis test results, but the utility of investigating persons with negative results has not been assessed. In this study, we used Bayesian latent class modeling to evaluate the sensitivity and negative predictive value (NPV) of PCR testing for *B. pertussis* to explore methods of increasing case ascertainment without using additional laboratory tests. The models were used to estimate the number of additional pertussis cases that could be identified by routinely investigating persons with negative pertussis test results during a recent interval of sporadic pertussis incidence (10.4 reported cases per 100,000 persons in 2010) in Wisconsin.

**MATERIALS AND METHODS**

**Study population**

Persons aged ≤18 years with suspected pertussis tested by PCR at laboratory A or B and reported to WIP during the period July 1, 2010–September 30, 2010, were included. The study population was limited to persons tested by laboratories A and B because only these laboratories consistently reported all positive, negative, and equivocal results for specimens tested for pertussis and tested all specimens for *Bordetella parapertussis*.

As part of WIP’s efforts to improve pertussis control in Wisconsin, children aged ≤18 years were included in the study because of morbidity risks and potential roles in spreading pertussis throughout the community. For age-based analyses, subjects were grouped to match standard school-level age ranges. Adults deemed high-risk were also investigated for prevention purposes but were excluded from the study to prevent selection bias.

This study was conducted as an extension of WIP’s normal surveillance activities and was determined by the University of Wisconsin–Madison institutional review board to be exempt from review.

**Laboratory testing**

Specimens submitted by Wisconsin health-care providers for *B. pertussis* testing were generally nasopharyngeal swabs. Laboratories A and B used a real-time PCR assay with a primer for nucleotide sequence IS481. Both laboratories note that *Bordetella holmesii* infection may also yield a positive result with this test. *B. parapertussis* testing was conducted using a primer for nucleotide sequence IS1001. A test result was considered equivocal if a specimen had a crossing threshold of >35 cycles and a repeat test of the specimen proved negative.

**Case investigation**

Parents of subjects aged <18 years with negative pertussis PCR tests, or the subjects themselves if aged 18 years, were contacted for phone interview. If the interview was incomplete after 3 phone contacts and a letter, the subject was determined to be unavailable. Data collected during the initial interview included: cough onset date and duration; the presence of paroxysms, whoop, or posttussive vomiting; alternate diagnosis by a health-care provider; and prescription of an antibiotic, date of initiation, and treatment duration. Subjects were classified on the basis of having received appropriate treatment for pertussis and experiencing an illness meeting or not meeting the Centers for Disease Control and Prevention’s (CDC’s) clinical case definition (CCD) for pertussis, defined as cough for ≥14 days with paroxysms, posttussive vomiting, or whoop and no likely alternative diagnosis (5). The CCD must be met (CCD+) for an illness to be considered a probable or confirmed case of pertussis (in the absence of a positive culture) according to CDC guidelines (5). PCR-negative CCD+ subjects were reported to the CDC accordingly.

If the initial interview revealed that the subject was CCD+, a full interview was conducted to collect information on demographic features, other symptoms, complications, vaccination history, epidemiologic links to laboratory-confirmed cases, possible sources of infection, and settings in which the person could have transmitted *B. pertussis*. All study subjects with positive PCR results for pertussis had initial and full interviews completed, as described above, by local health department staff.

All information was entered and stored in the Wisconsin Electronic Disease Surveillance System database, an online disease investigation and reporting system.

**Statistical analysis**

Analyses were conducted using SAS software (version 9.1.3; SAS Institute, Inc., Cary, North Carolina) and OpenBUGS software (version 3.2.1) (15).

Validity measures of PCR (sensitivity, specificity, positive predictive value (PPV), and NPV) and their associated
95% exact binomial confidence intervals were calculated. Meeting the CCD was used as the standard in calculating the validity measures for PCR, because other standards for pertussis disease were not available in this population. Specifically, PCR could not be compared with culture, serology, or epidemiologic links, because cultures were rarely performed, a standardized serological assay was not in use, and the frequency of confirmatory epidemiologic links to laboratory-confirmed cases was low. Because the CCD is not a true gold standard for the existence of pertussis infection (11), κ values and 95% confidence intervals were also calculated to measure the agreement between PCR and CCD.

*B. pertussis* bacterial load is greatest early in the illness, and the ability of PCR to detect infection declines as bacterial load decreases over time (16). Therefore, testing delay—the time elapsed between cough onset and specimen collection for PCR testing—was considered as a potential modifier of the relationship between PCR result and meeting the CCD. Descriptive statistics suggested that the greatest impact of test timing on PCR positivity occurred between specimens collected ≤7 days after cough onset and specimens collected >7 days after cough onset. A testing delay less than or equal to 3 weeks was also examined, based on CDC guidelines for PCR testing (5).

The effect of nonresponse (unavailability for interview) on the validity and κ measures was assessed, but the inclusion of nonrespondents did not change statistical significance. Assuming that nonrespondents did not meet the CCD did not change the sensitivity estimate of PCR, increased the NPV of PCR by only 4%, and increased κ between PCR and the CCD by 0.02. Thus, nonrespondents were excluded from the final analysis.

A Bayesian latent class modeling approach was used to calculate adjusted estimates of validity measures for PCR in the absence of a gold standard (13, 17). Briefly, the Bayesian latent class modeling proceeded in 2 steps. First, a literature review was conducted to determine appropriate prior distributions of the sensitivity and specificity of PCR and CCD in identifying pertussis cases. Only studies that included raw subject data for CCD and PCR assay results using a primer that targeted nucleotide sequence IS481 were included (6–8, 18–40). Studies were excluded from the literature review if they did not include children aged ≤18 years or if the majority of samples for PCR or culture were collected more than 3 weeks after symptom onset. Sensitivity and specificity measurements were calculated for each study in up to 4 categories: PCR evaluated using culture, PCR evaluated using various methods, CCD evaluated using culture, and CCD evaluated using various methods. For the category of PCR evaluated using various methods, we excluded use of confirmatory or nested PCR as part of the standard for evaluating the primary IS481 PCR analysis in order to ensure independence of the calculated measurements. When multiple methods were used to evaluate PCR or CCD, such as both culture and serum samples, subjects testing positive by either method were considered positive for pertussis in the calculations. The results of the literature review are presented in Table 1.

Beta distributions were used to specify the prior distributions for the sensitivity and specificity of PCR and CCD. We conducted a meta-analysis using a β-binomial model and data from the literature review presented in Table 1 to determine the parameters of the β prior distributions for the sensitivity and specificity of PCR and CCD (41). The details of this analysis are presented in Web Appendix 1 (available at http://aje.oxfordjournals.org/). Two Bayesian latent class models were created on the basis of prior distributions reflecting different standards used to evaluate PCR or the CCD. The “classic pertussis” model considered only studies in which culture alone was used to evaluate PCR or CCD. The “all pertussis” model considered studies that evaluated PCR or the CCD using serological assays, combinations of clinical and epidemiologic evidence, PCR (for studies evaluating the CCD), or any combination of the above with or without culture. Including confirmatory criteria not based on bacterial load was believed to represent both mild and classic disease.

The prevalence of pertussis in a nonoutbreak setting among coughing or reported individuals is population-dependent, so a noninformative uniform prior distribution was used for prevalence. After the prior distributions were determined, the posterior knowledge on the validity measures of PCR and CCD was obtained by combining the prior information with the information obtained from the data using Bayes’ theorem. The posterior distributions of the validity measures were calculated based on the current study data, the likelihood function from the multinomial model of the latent class model, and the joint prior distribution over all diagnostic test validity measures. Because the posterior distribution is not in closed form, the Gibbs sampling technique with 10,000 iterations and a burn-in period of 1,000 iterations was used to derive samples for the marginal posterior density for each parameter (13). Convergence was assessed using the Gelman and Rubin test and by evaluating the trace plots for each parameter (42). The median values of the posterior distributions were used as the point estimates for all validity measures and are reported with corresponding 95% Bayesian credible intervals. In addition to validity measures calculated for PCR and CCD, the Bayesian latent class models also estimated the prevalence of true *B. pertussis* infection among persons with illnesses reported to the WIP.

The PCR and CCD evaluations were expected to be conditionally independent, since the outcome of the PCR test was independent of the CCD assessment; therefore, we used a Bayesian latent class model with conditional independence between tests to analyze our study data (14). To verify the assumption of conditional independence between PCR and CCD, we also performed an analysis using a Bayesian latent class model that allows for conditional dependence between tests (17). We assessed the conditional independence assumption by evaluating the covariance parameters between the 2 tests of the conditional dependent model and by comparing the Deviance Information Criterion values of the 2 models (43).

We conducted a sensitivity analysis to assess the impact of using different sets of prior distributions for sensitivity, specificity, and prevalence on the estimation of the validity measures. The analysis was conducted for the “classic pertussis” model and the “all pertussis” model, as described above. We also examined the effect of a testing delay of ≤7 days.
compared with testing delays of >7 days by generating stratified models.

RESULTS

Study population

During the study period, among 664 suspected pertussis cases reported to the WIP, 350 (53%) occurred in persons aged ≤ 18 years (Figure 1). Of those, 150 (43%) were tested by laboratory A, 102 (29%) by laboratory B, and 26 (7%) by other laboratories; for 72 cases (21%), there was no record of a laboratory test. Among suspected cases tested by laboratory A or B, 225 (89%) were tested using PCR only, 25 (10%) were tested using PCR and culture, and 2 (1%) were tested using culture only. Laboratory A identified only 3 positive test results for *B. parapertussis* and laboratory B only 1 case, which was also positive for *B. pertussis*. Based on the proportion of positive test results reported by laboratories A and B, we estimate that these laboratories conducted 40% (38 of 96 reported PCR-positive results) of the pertussis testing in Wisconsin during the study period.

Among the final study population of 250 children meeting inclusion criteria, 24 had positive pertussis PCR results and 226 had negative or equivocal results. Persons with equivocal results were grouped with PCR-negative subjects for subsequent analysis. All PCR-positive subjects were interviewed; we were able to reach 190 (84%) PCR-negative subjects for an interview. Among PCR-negative children, fewer females (79%) than males (90%) were successfully interviewed (*P* = 0.024). Although 25 PCR-tested samples were also tested using culture, culture results were not included in our analyses. Seventy-one percent of PCR-positive children were CCD+ (Table 2). PCR-positive children were significantly more likely than children with negative tests to have cough lasting ≥ 2 weeks (91% vs. 64%) and paroxysms, whoop, or posttussive vomiting (79% vs. 47%). Forty percent of PCR-positive children versus 10% of PCR-negative children had epidemiologic links to laboratory-confirmed cases. This difference persisted when only CCD+ children were compared (33% of PCR-positive children vs. 8% of PCR-negative children). Receiving treatment appeared to correspond to the PCR result, not clinical symptoms, since 100% of PCR-positive

| Table 1. Prior Distributions of Sensitivity and Specificity Measures for Pertussis Polymerase Chain Reaction and the Pertussis Clinical Case Definition From a Literature Search and Associated Bayesian Latent Class Model Parameters for the “Classic Pertussis” and “All Pertussis” Models |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Validity Measure               | Parameter, %    | α   | β   | Reference Nos. | No. of Studies |
|                                | Median | IQR |     |                |                |
| Detecting Classic Pertussis    |         |     |     |                |                |
| Sensitivity                    | 97.5    | 88  | 100 | 7.9            | 0.7            | 6, 7, 19, 20, 23–31, 33–37 | 18         |
| Specificity                    | 90      | 85  | 93  | 12.0           | 2.0            | 7, 8, 22, 33         | 4          |
| Sensitivity CCD                | 100     | 99  | 100 | 20.0           | 2.0            | 7, 8, 22, 33         | 4          |
| Specificity CCD                | 41.5    | 30  | 60  | 1.5            | 1.5            | 7, 18, 21, 22, 32, 38, 39 | 7          |
| Prevalence CCD                 | 1.0      | 1.0 |     |                |                | 7, 18, 21, 22, 32, 38, 39 | 7          |
| Detecting All Pertussis        |         |     |     |                |                |
| Sensitivity                    | 46.5    | 35  | 52  | 19.0           | 24.0           | 7, 20, 25, 26, 33, 40 | 6          |
| Specificity                    | 93      | 92  | 97  | 14.0           | 1.0            | 7, 20, 25, 26, 33, 40 | 6          |
| Sensitivity CCD                | 74      | 52  | 93  | 1.3            | 0.5            | 7, 18, 21, 22, 32, 38, 39 | 7          |
| Specificity CCD                | 54      | 42  | 51  | 1.6            | 1.2            | 7, 18, 21, 22, 32, 38, 39 | 7          |
| Prevalence CCD                 | 1.0      | 1.0 |     |                |                | 7, 18, 21, 22, 32, 38, 39 | 7          |

Abbreviations: CCD, clinical case definition; IQR, interquartile range; PCR, polymerase chain reaction. α and β refer to the parameters of the β distribution and were determined using a meta-analysis based on the β-binomial model for overdispersed binomial data using the data from the cited literature, except for the CCD measures for the “classic pertussis” model, which lacked a sufficient number of studies to fit a β-binomial model (41). The method of moments was used to calculate the β distribution parameters for the CCD measures for the “classic pertussis” model. Median sensitivity/specificity across studies. 25th–75th percentile range of sensitivity/specificity across studies. A priori, very little was known about the true prevalence of pertussis in this population. Hence, a noninformative prior distribution was used to model the uncertainty in the prevalence, that is, α = 1 and β = 1 (uniform distribution).
CCD+ children were treated versus 62% of PCR-negative CCD+ children.

Among the 63 PCR-negative subjects who experienced ≥2 weeks of cough with paroxysms, whoop, or posttussive vomiting, 9 (14%) had an alternate diagnosis (Mycoplasma (n = 3), allergies/asthma, Chlamydia pneumoniae, mononucleosis, respiratory syncytial virus, “walking pneumonia,” or Streptococcus) and thus had illnesses not meeting the CCD. Only 26% of PCR-negative CCD+ subjects were tested during the first week of their illness, compared with 62% of PCR-negative subjects without illnesses meeting the CCD (Table 2). The frequencies of epidemiologic links to laboratory-confirmed cases were similar among PCR-negative subjects with and without illnesses meeting the CCD.

Measures of validity

The unadjusted validity measures from pertussis PCR testing are presented in Table 3. The sensitivity of PCR was very low; of 71 CCD+ subjects, only 17 cases (24%) were detected using PCR. Subjects with illnesses not meeting the CCD accounted for 136 of the 190 negative PCR tests, yielding an NPV of 72%. Kappa also demonstrated very poor agreement between the PCR result and the CCD (κ = 0.23, 95% confidence interval: 0.11, 0.35).

In unadjusted analyses, the NPV of PCR varied with testing delay. PCR tests conducted on specimens collected ≤7 days after cough onset had a significantly higher NPV than PCR tests conducted on specimens collected >7 days after cough onset (84% vs. 52%; P < 0.05) (Table 4). All differences observed when examining a 3-week testing delay were accounted for by tests performed on specimens collected ≤7 days after cough onset.

Adjusted estimates for sensitivity and specificity

The Bayesian latent class model approach was used to calculate adjusted estimates for sensitivity and specificity. For both the “classic pertussis” model and the “all pertussis” model, the differences in Deviance Information Criterion values between the conditional independent and dependent models were very small, and none of the covariance parameters between tests for the conditional dependent model were significantly different from 0 (Web Appendix 2). Hence, the conditional independent model was adopted for the primary analysis.

The validity measures from the “classic pertussis” and “all pertussis” models are shown in Table 3. After correcting for the previously documented sensitivity and specificity of PCR and the CCD, the sensitivity and NPV of PCR were higher than the uncorrected measures. The sensitivity estimates for PCR differed significantly between the “classic pertussis” and “all pertussis” models: 94% (95% Bayesian credible interval (BCI): 63, 100) for the “classic pertussis” model versus 43% (95% BCI: 29, 58) for the “all pertussis” model. However, there was no significant difference in the NPV of PCR between the “classic pertussis” (NPV = 99%, 95% BCI: 95, 100) and “all pertussis” (NPV = 87%, 95% BCI: 71, 95) models. The NPV of the CCD was almost maximized in both models (classic pertussis: 99%; all pertussis: 96%), but the PPV was very low: 22% (95% BCI: 11, 40) for the “classic pertussis” model and 53% (95% BCI: 26, 89) for the “all pertussis” model.
The models revealed no statistically significant difference in NPV between the first week and subsequent weeks after the data were stratified by testing delay (Table 4). In the “classic pertussis” model, the CCD was significantly less specific when PCR testing was conducted after the first week of illness, but there was no significant difference in predictive value.
Using the “classic pertussis” model, the prevalence of pertussis was estimated at 8% (95% BCI: 4, 15) among persons with illnesses reported to WIP. The prevalence using the “all pertussis” model was estimated at 21% (95% BCI: 10, 38).

Finally, a sensitivity analysis was performed using various alternative sets of prior distributions for model parameters (Web Appendix 3). The estimates obtained from the Bayesian latent class model were fairly robust to changes in the prior distributions.

**DISCUSSION**

This study examined the likelihood of *B. pertussis* infection occurring among children with negative PCR testing. One in 4 subjects with negative PCR results were CCD+ and therefore met the CDC’s probable case definition (5). In unadjusted analyses, this corresponded to lower sensitivity for PCR in comparison with previous reports (6, 8, 11, 19, 20, 23–31, 33–37). Because the CCD is believed to have low specificity (8), we corrected our validity measures using Bayesian latent class modeling for different severities of pertussis disease.

The “classic pertussis” model only included studies of persons who had *B. pertussis* detectable by culture, excluding infected persons with bacterial loads that were insufficient for detection. The “all pertussis” model attempted to remedy this deficiency by including studies with a variety of standards for evaluating PCR and the CCD, especially serological evidence. Because serological and epidemiologic evidence are not dependent on nasopharyngeal bacterial load at the time of sampling, the prior distributions of PCR and CCD sensitivity and specificity for the “all pertussis” model reflect a broader clinical range of pertussis. This provides a more complete picture of clinically and epidemiologically important disease.

The adjusted validity measures in our study offer a clearer picture of the outcome from investigating PCR-negative subjects. When assessing disease detectable by culture, the 99% NPV of PCR indicates that a negative PCR result reliably predicts an absence of “classic” pertussis. These results suggest that it would be inefficient for local health departments to investigate all persons with negative test results if classic pertussis is the outcome of interest, because 100 illnesses would need to be investigated to identify a single case. If local health departments are also interested in detecting mild disease, the 87% NPV of the “all pertussis” model indicates that investigating PCR-negative subjects would identify more pertussis cases, with 8 PCR-negative subjects needing to be investigated to identify 1 true case of pertussis of any severity.

Time from symptom onset to specimen collection is known to affect the observed sensitivity of PCR in detecting *B. pertussis* (37). Thus, the CDC recommends testing within 3 weeks of symptom onset. In the unadjusted results, a negative PCR result was more predictive of not meeting the CCD if the specimen was collected during the first week of the illness, compared with subjects who had had cough for at least 1 week when the specimen was collected. However, the adjusted models did not statistically support the same conclusion from negative PCR results obtained during the first week.
Table 4. Unadjusted and Adjusted Measures of Validity (%) for Pertussis Polymerase Chain Reaction Testing and the Pertussis Clinical Case Definition Among Children Reported to Have Pertussis, According to Testing Delay, Wisconsin, July 1, 2010–September 30, 2010

<table>
<thead>
<tr>
<th></th>
<th>Tested at ≤7 Days (n = 94)</th>
<th>Tested at &gt;7 Days (n = 100)</th>
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<tr>
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<td>Estimate 95% CI/BCIa</td>
<td>Estimate 95% CI/BCIa</td>
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<td><strong>Unadjusted analyses (PCRb)</strong></td>
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<tr>
<td>Sensitivity</td>
<td>22 (6, 48)</td>
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<tr>
<td>Specificity</td>
<td>95 (87, 99)</td>
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<td>PPV</td>
<td>50 (16, 84)</td>
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<tr>
<td>NPV</td>
<td>84 (76, 92)</td>
<td>52 (42, 63)</td>
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<tr>
<td><strong>Classic pertussis modelc</strong></td>
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<td>PCR</td>
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<tr>
<td>Sensitivity</td>
<td>92 (76, 99)</td>
<td>93 (79, 99)</td>
</tr>
<tr>
<td>Specificity</td>
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<td>NPV</td>
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<td>98 (92, 100)</td>
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<td><strong>All pertussis modeld</strong></td>
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<tr>
<td>PCR</td>
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<tr>
<td>Sensitivity</td>
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<td>42 (29, 57)</td>
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<tr>
<td>Sensitivity</td>
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<td>PPV</td>
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<td>NPV</td>
<td>97 (78, 100)</td>
<td>94 (66, 100)</td>
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Abbreviations: BCI, Bayesian credible interval; CCD, clinical case definition; CI, confidence interval; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value.

* P < 0.05 (tested at ≤7 days vs. tested at >7 days).

a Confidence intervals were used for the unadjusted measures. Credible intervals were generated for the adjusted models. Unadjusted measures for PCR were calculated using the CCD as the standard; no unadjusted measures for the CCD were calculated.

b The “classic pertussis” model used evaluations of the validity measures against culture. The median values of the posterior distributions were used as the point estimates for the validity measure.

c The “classic pertussis” model used evaluations of the validity measures against a variety of criteria, including serology and epidemiologic features. The median values of the posterior distributions were used as the point estimates for the validity measure.

d The “all pertussis” model used evaluations of the validity measures against a variety of criteria, including serology and epidemiologic features. The median values of the posterior distributions were used as the point estimates for the validity measure.

Our adjusted results also highlight the need to reassess the CCD, because it lacks specificity (11). From our calculated PPV, only 22% of CCD+ persons have pertussis that would be detectable by culture. When considering both mild and severe disease, a CCD+ individual is just as likely as not to have pertussis. This suggests that the currently accepted CCD misclassifies many persons without true pertussis as having pertussis. Refinements to the CCD, such as the age-based definitions suggested by Cherry et al. (44), should be considered to increase its specificity.

While the major deficiency associated with the CCD is its lack of specificity, 30% of PCR-positive children had illnesses that did not meet the CCD. Both Bayesian latent class models in our study estimated the NPV of the CCD at above 95% but the PPV of PCR at below 80%. Therefore, the CDC’s confirmed case definition appeared to be correct in excluding PCR-positive children with illnesses not meeting the CCD in our sample.

Because this study was based on data obtained during routine public health surveillance, it was limited to subjects who sought medical care, were tested by health-care providers, and were available for follow-up. Because of the small sample size, confidence intervals for many measures were wide, potentially masking differences that would emerge from a larger sample, and meaningful stratifications were limited. Our study was particularly limited by the inability to stratify by age group, because PCR sensitivity differs among children aged ≤18 years (6).

The results derived from Bayesian latent class models are dependent on the quality of information used to create them. Narrow, well-substantiated prior distributions for the model parameters are important for confident interpretations of the results (13). Because the literature validating the CCD is limited, the prior distributions of the validity measures were only vaguely informative with large variances. This is reflected in the wide Bayesian credible intervals of some results. Still, sensitivity, specificity, and prevalence estimates generated by the models were similar to those noted in other studies (1, 3, 11).

The results of this study may not be generalizable to test results obtained from laboratories that use different PCR testing methods. Additionally, because pertussis PCR results, clinical signs and symptoms, and bacterial load may differ between children and adults (1, 6, 10), the results of our study may not apply to persons over age 18 years. During an outbreak, the NPV would decrease because of the increased disease prevalence, so our results should not be applied to situations with substantially different pertussis prevalence.

Investigating all children with negative pertussis PCR results reported to WIP considerably increased the number of cases Wisconsin reported to the CDC as cases of probable or confirmed pertussis. This finding substantiates the CDC’s recommendation that providers should not rule out pertussis infection based solely on a negative PCR result. Instead, a negative test result should be interpreted with consideration of the patient’s signs and symptoms and available epidemiologic information to avoid missing cases. The value of investigating all persons with negative results should be weighed against the costs of follow-up and concerns regarding antibiotic resistance. Known contacts of pertussis patients and
infants should be among people prioritized for follow-up among PCR-negative persons. Further study is necessary to determine whether routine investigation and follow-up of these or other specific PCR-negative groups would result in better disease control, not just increased detection.

Using Bayesian latent class modeling allowed a deeper examination of pertussis PCR tests performed on Wisconsin children during a relatively short period. With only a PCR result and clinical symptoms available in most cases, this model’s incorporation of published information provides a context for case evaluation by estimating prevalence and predictive values.

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