Observational Study

Medicine®

OPEN

Bordetella parapertussis outbreak in Southeastern Minnesota and the United States, 2014

Vytas P. Karalius, MPH, MA[a], Stefanea L. Rucinski, BS[b], Jayawant N. Mandrekar, PhD[c], Robin Patel, MD[b,d,*]

Abstract

Whooping cough is traditionally ascribed to *Bordetella pertussis*; however, *Bordetella parapertussis* can cause a similar clinical syndrome. This study describes an outbreak of *B. parapertussis* in Southeastern Minnesota and the United States (US) in 2014. This was a retrospective analysis of Mayo Clinic and Mayo Medical Laboratories patients who tested positive for *B. parapertussis* from 2012 to 2014. The medical records of Mayo Clinic patients who tested positive in 2014 were reviewed for demographic information, presenting symptoms, disease course, and vaccination history. In Southeast Minnesota, 81% of the 31 patients who tested positive for *B. parapertussis* in 2014 were found to be positive from October through December. Their mean age was 5.9 years. Five reported "exposure to pertussis." Two pairs of siblings were affected. Patients reported having had symptoms for an average of 2.6 weeks before nasopharyngeal specimen collection for *B. parapertussis* testing. Cough was the primary symptom reported. Forty percent reported posttussive vomiting, 40% coryza, 32% apnea/sleep disturbance, and 12% sore throat. All were current with pertussis vaccination. Based on the review of national data, an outbreak occurred nationally in the Northeast and Midwest US over the same time period. In 2014, there was an outbreak of *B. parapertussis* in Southeastern Minnesota and likely other parts of the US. The presenting illness was similar to that of *B. pertussis.* All patients were vaccinated against pertussis, suggesting that pertussis vaccination is ineffective against *B. parapertussis*.

Abbreviations: *B. parapertussis* = *Bordetella parapertussis*, *B. pertussis* = *Bordetella pertussis*, CDC = Centers for Disease Control and Prevention, PCR = Polymerase Chain Reaction.

Keywords: *Bordetella*, Minnesota, outbreak, parapertussis, pertussis

1. Introduction

Pertussis or whooping cough is a disease that has been increasing in prevalence in the United States (US) over the last 25 years.[1–4] From 2010 through 2013, there were over 123,000 cases of pertussis documented in the US.[4–7] While the primary etiologic agent of whooping cough has been considered to be *Bordetella pertussis*, a similar illness can be caused by *Bordetella parapertussis*.[3] *B. parapertussis* is generally considered to cause disease with milder symptoms; however, children with *B. parapertussis* infection can present with typical whooping cough symptoms, including prolonged cough, paroxysms, whooping, and posttussive vomiting.[3,8–10] As interest in whooping cough has grown, it has become apparent that *B. parapertussis* is more prevalent than previously assumed and that it may be contributing to the overall pertussis burden.[8,10,11]

While vaccination against pertussis has become ubiquitous in most developed countries using acellular (as in the US) or whole-cell *B. pertussis* vaccines, it has become increasingly clear that neither provides protection against *B. parapertussis*.[9–13] This may be in part due to the fact that the vaccines currently contain antigens from *B. pertussis* only,[12] and that *B. parapertussis* can evade human immune responses[14–19]; paradoxically, *B. pertussis* vaccine itself may increase host susceptibility to *B. parapertussis*.[12,20]

Little is known about the epidemiology of *B. parapertussis*. It has been suggested to have a 4-year cycle,[21] with no seasonality[8]; however, it appears that outbreaks can occur.

Reports of outbreaks of *B. parapertussis* have increased in the recent literature. In 2010, an outbreak of 3 *Bordetella* species—*B. pertussis, B. parapertussis*, and *B. holmesii*—was reported, in which clinical features at presentation did not allow for clear differentiation of etiology.[22] In the winter months of 2011 to 2012, an outbreak of *B. parapertussis* with pertussis-like illness occurred in Wisconsin.[23] Reports of *B. parapertussis* have increased not just in the US, but also globally,[24–27] with *B. parapertussis* now being the dominant species in Europe and the Middle East.[24,25,28]

Overall, it has become apparent that, while mass vaccination campaigns have existed globally for over 50 years, the incidence of pertussis/whooping cough is increasing in developed countries and remains a problem of clinical significance. This is a result of not just *B. pertussis*, but also *B. parapertussis*. The objective of

Editor: Patrick Wall.

RP has a patent on Bordetella pertussis/parapertussis PCR. VPK received an Infectious Disease Society of America 2016 Medical Scholar scholarship to perform the research presented.

Presented in part at the 55th Interscience Conference of Antimicrobial Agents and Chemotherapy, San Diego, CA, 2015.

The authors have no funding and conflicts of interest to disclose.

[a] Mayo Clinic School of Medicine, [b] Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology, [c] Division of Biomedical Statistics and Informatics, Department of Laboratory Medicine and Pathology, [d] Division of Infectious Disease, Department of Medicine, Mayo Clinic, Rochester, MN.

[*] Correspondence: Robin Patel, Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (e-mail: patel.robin@mayo.edu).

Medicine (2017) 96:20(e6730)

Received: 5 December 2016 / Received in final form: 3 April 2017 / Accepted: 6 April 2017

http://dx.doi.org/10.1097/MD.0000000000006730

the present study was to describe an outbreak of *B. parapertussis* in 2014 in Minnesota; as shown by the data presented, other parts of the US were likely affected.

2. Materials and methods

2.1. Design

The Mayo Clinic Institutional Review Board approved this study. The study was a retrospective cohort study of patients who tested positive for *B. parapertussis*.

2.2. Study population

Mayo Clinic Rochester is the primary provider of healthcare for a large area of Southeastern Minnesota. Mayo Medical Laboratories is a reference laboratory that tests patients from around the country. To examine whether the outbreak witnessed in Southeast Minnesota was a localized event, or an event extending beyond Southeastern Minnesota, reference laboratory data were examined. All patients, from Southeastern Minnesota and nationally, who tested positive or negative for *B. parapertussis* by polymerase chain reaction (PCR) performed on nasopharyngeal specimens from December 2011 through December 2014 were identified. Parapertussis cases were defined as patients with PCR positive for *B. parapertussis*. For patients who tested positive for *B. parapertussis* between January and December 2014 in Southeastern Minnesota, the electronic medical records were reviewed for demographics, symptomology, medical history, and vaccination history (Minnesota Statute 144.335). For the national patients, information was collected as to date and location of nasopharyngeal collection for both positives and negatives from December 2011 through December 2014.

2.3. PCR for B. parapertussis

Nasopharyngeal swabs were submitted by healthcare provider request for *B. pertussis/B. parapertussis* PCR. Nasopharyngeal swab samples were placed into tubes with neutralization buffer and subjected to heat lysis on a Thermomixer R (Eppendorf AG; Hamburg, Germany) for 6 minutes at 99°C and 1400 rpm, followed by centrifugation for 20 seconds at $20{,}800 \times g$. Then, 5 μL of the supernatant was combined with 15 μL of PCR master mix and tested using a previously described duplex PCR assay targeting IS*481* and IS*1001* for *B. pertussis* and *B. parapertussis* detection, respectively.[29]

2.4. Medical record review and analysis for Southeast Minnesota

Electronic medical records of the study population from Mayo Clinic Rochester were reviewed for the following variables: age at onset of disease, date of birth, sex, duration of symptoms before presentation to a healthcare professional, report of any contact with pertussis, documented cough symptoms (and whether the cough was productive or not), nasal symptoms (coryza, rhinorrhea, or congestion), sore throat, fever, posttussive emesis, and apnea. Information on related medical history was also recorded, including history of asthma, chronic obstructive pulmonary disease, and tobacco exposure. Dates of pertussis vaccine administration and whether a patient was "up-to-date" with pertussis vaccine (i.e., had received the correct number of pertussis vaccinations as suggested by the Centers for Disease Control and Prevention [CDC]) were recorded. Information on treatment was collected, including pharmacological treatment by healthcare personnel, recurrence of symptoms resulting in another visit within 6 months and prior visits with a missed diagnosis.

2.5. Statistical analyses

Means and percentages were calculated for demographic and descriptive data in patients from Mayo Clinic Rochester. The percent positive rate was calculated at the national level and in Southeastern Minnesota. The national data were further divided into 10 regions based on geographic groupings used by the US Department of Health and Human Services and (for influenza surveillance) by the CDC as follows:

1. Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont
2. New Jersey and New York
3. Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, and West Virginia
4. Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, and Tennessee
5. Illinois, Indiana, Michigan, Ohio, and Wisconsin
6. Minnesota only
7. Arkansas, Louisiana, New Mexico, Oklahoma, and Texas
8. Iowa, Kansas, Missouri, and Nebraska
9. Colorado, Montana, North Dakota, South Dakota, Utah, and Wyoming
10. Arizona, California, Hawaii, and Nevada
11. Alaska, Idaho, Oregon, and Washington.

CDC region 5 was divided into solely Minnesota (5′) and the rest of region 5 (5) to prevent skewing of region 5 data by Minnesota, as approximately 60% of samples from region 5 were from Minnesota. The percent positivity, mean, number of total tests performed, and confidence interval were displayed graphically.

3. Results

The percent positivity of nasopharyngeal specimens for *B. parapertussis* in Southeastern Minnesota is shown in Fig. 1. In 2012, there were a total of 23 patients who tested positive for *B. parapertussis* and in 2013, a total of 2 patients. Thirty-one patients tested positive for *B. parapertussis* in 2014; of these, 81% (25) tested positive from October through December.

Of the 31 positive patients in 2014, 25 consented to have their records reviewed (Minnesota Statute 144.335). Patient age ranged from less than 1 to 11 years (mean 5.9 years), and 14 (56%) were male. Five patients reported "exposure to pertussis." Four reported a family member with "pertussis." Two pairs of siblings were affected. Patients presented for medical evaluation with an average duration of symptoms of 2.6 weeks before testing. All reported cough as their primary symptom. Ten (40%) reported posttussive vomiting, 10 (40%) coryza, 8 (32%) apnea/sleep disturbance, and 3 (12%) sore throat. At the time of examination, all patients were afebrile.

Twenty-two of 25 patients were prescribed azithromycin. Three were not given antibiotic therapy, as they were considered as being past the antibiotic treatment window.

Seven were diagnosed or treated for another disease or condition considered to be causing their cough before the visit with nasopharyngeal swab confirmation of *B. parapertussis*. These conditions included croup, "chronic cough," bronchitis,

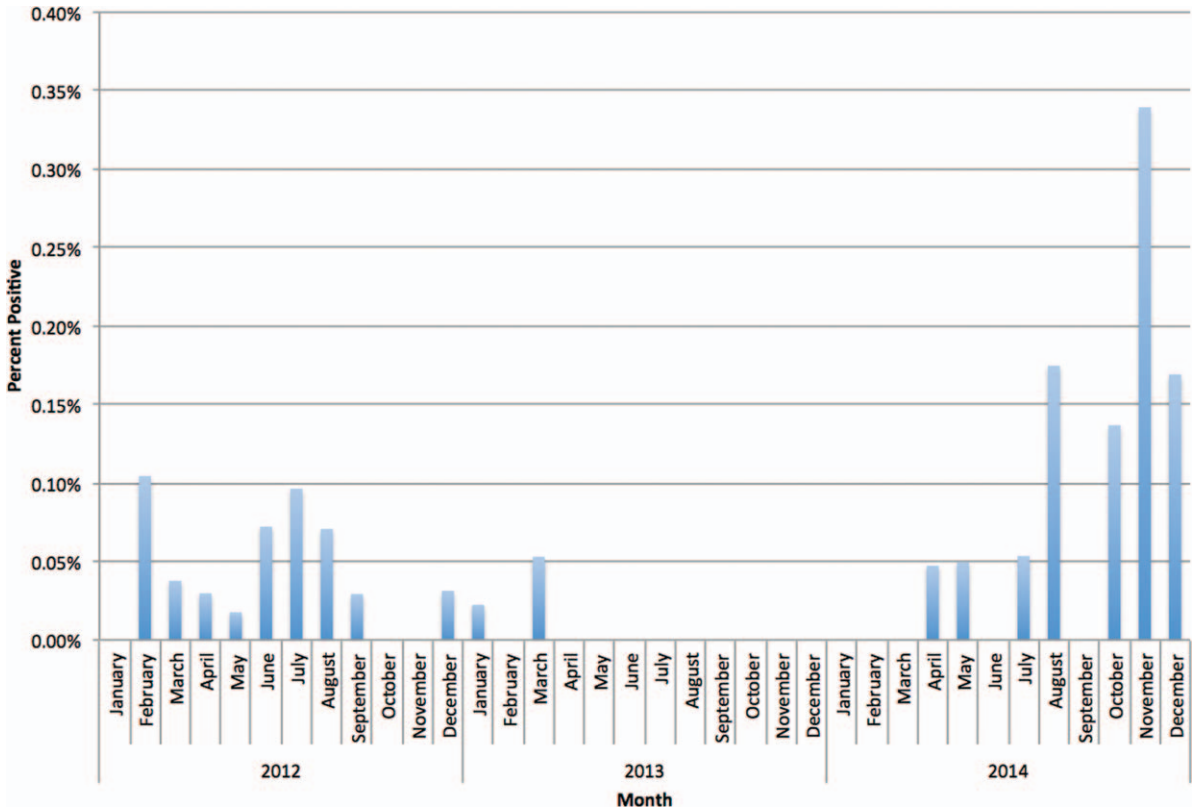

Figure 1. Percent positivity of the *B. parapertussis* polymerase chain reaction assay in Southeastern Minnesota by month, January 2012 to December 2014.

"post-viral cough," "cough NOS," and exacerbated asthma. In these cases, treatment included dexamethasone, amoxicillin, albuterol, and/or steroids. Three patients had medical appointments for continued respiratory/cough symptoms in the 6 months following *B. parapertussis* diagnosis; 1 was evaluated for an upper respiratory tract infection 2 months after diagnosis, 1 was evaluated for an upper respiratory tract infection 1 and 4 months after diagnosis, and 1 was evaluated for "cough" at 3 and 4 months following *B. parapertussis* diagnosis (due to continued symptoms). Overall however, patients improved and symptoms resolved. All patients were "up to date" with pertussis vaccination as recommended by the CDC.

The percent positivity for *B. parapertussis* on a national scale (using reference laboratory data) is shown in Fig. 2. From December 2011 through December 2014, 120,113 patients were tested via PCR for *B. parapertussis*, of which 1098 were positive. An increase in percent positivity was observed starting in July 2014 and continued through December 2014. Figure 3 shows the national reference laboratory data by geographic region. There was a sizeable increase in the percent positivity in regions 1, 2, 3, 5, 5′, and 7. Comparing the percent positivity from April through December 2014 between regions, regions 8, 9, and 10 were not significantly different from each other but were significantly different ($P < .05$) from all other regions, except region 4. This further suggests that they did not experience the same increased incidence as the other regions.

4. Discussion

There was an outbreak of *B. parapertussis* in Southeastern Minnesota in late 2014. As shown in Fig. 1, there was an increase in cases in the months of October through December

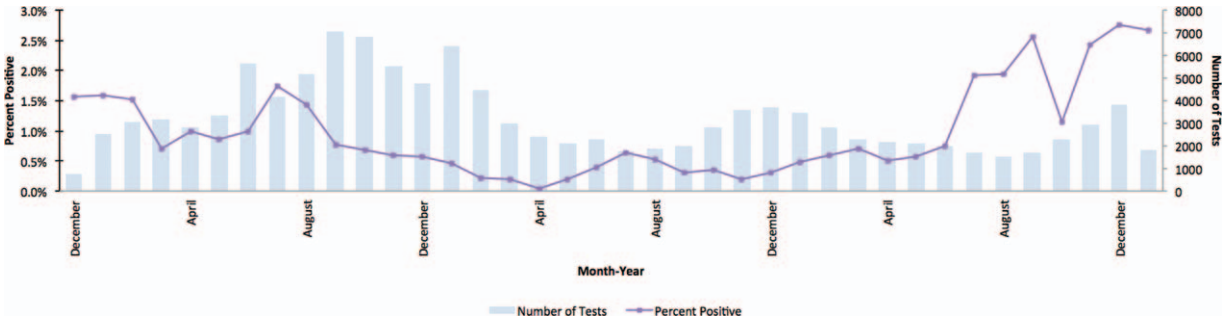

Figure 2. Percent positivity of the *B. parapertussis* polymerase chain reaction assay nationally using Mayo Medical Laboratories reference laboratory data (December 2011–2014).

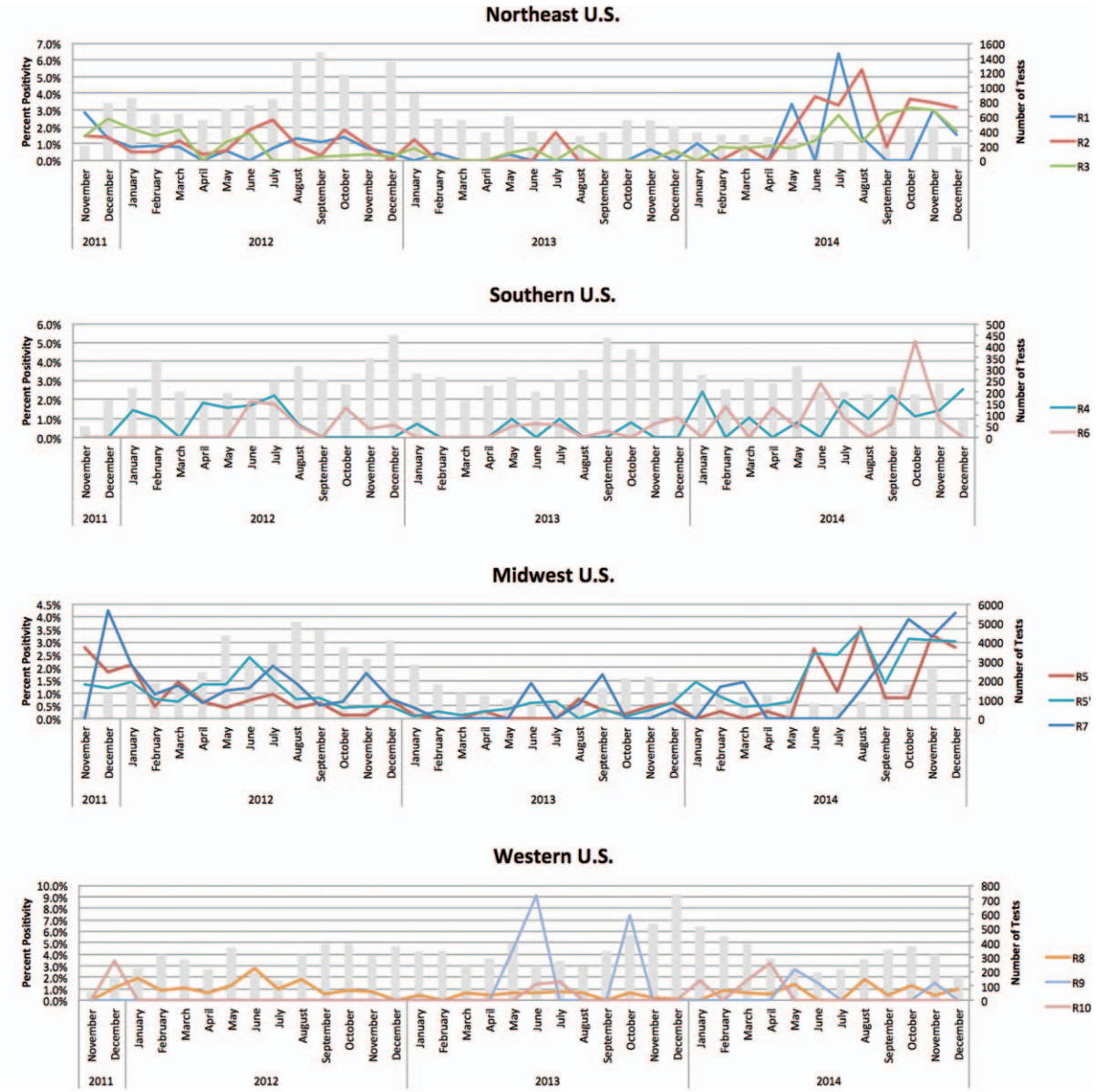

Figure 3. Percent positivity of the *B. parapertussis* polymerase chain reaction assay by geographic areas of the United States (R1 is Region 1, R2 is Region 2, etc.).

of 2014. In addition, the increased percent positivity from regions 1, 2, 3, 5, 5′, and 7 suggests that this outbreak was not unique to Southeastern Minnesota but extended to the Northeast and Midwest US, while sparing the Southwest and West Coast.

While originally considered as a cause of less severe whooping cough, it is becoming increasingly accepted that *B. parapertussis* can cause typical pertussis symptomology. In the present study, symptoms were similar to those expected with *B. pertussis*. This is consistent with recent literature suggesting that *B. parapertussis* infection presents as typical whooping cough.[3,8–10] This suggests that symptoms alone should not be used to make a distinction between *B. pertussis* and *B. parapertussis*. More importantly, it supports testing for both *B. pertussis* and *B. parapertussis* together in patients with whooping cough symptomatology.

It should also be noted that all patients in Southeastern Minnesota with *B. parapertussis* were vaccinated against pertussis, suggesting that pertussis vaccination is ineffective against *B. parapertussis*, consistent with most of the recent literature.[11–13,17,20] Redevelopment of the pertussis vaccination has become a topic of considerable discussion, with new approaches being studied.[30,31] Our findings suggest that *B. parapertussis* should be considered when developing new pertussis vaccines. Also of note is that the average age of patients with *B. parapertussis* was much younger than those with *B. pertussis*. During a 2012 *B. pertussis* outbreak in a similar population in Southeastern Minnesota, we found that the average age of patients with *B. pertussis* was 15.6 years.[32] This contrasts with the mean age in the present study population which was 5.9 years, underscoring the lack of activity of the current vaccination strategy against *B. parapertussis*.

This and other recent studies highlight the importance of *B. parapertussis* surveillance, and possibly surveillance for other related species, as causes of cough illness. Unlike *B. pertussis*, *B. parapertussis* is not considered a nationally notifiable disease by the Nationally Notifiable Disease Surveillance System of the CDC. Only a positive test for *B. pertussis* (PCR or isolation from clinical specimen) is considered a criterion for diagnosis of pertussis. The data presented herein suggest that *B. parapertussis* should be considered for inclusion in this definition.

An accepted practice for passive detection of *B. pertussis* is to actively search for and notify potential cases (e.g., household, family, daycare, healthcare workers, and other close contacts). This can lead to a significant increase in detection.[33] The recent literature, as well as the present study findings that siblings were positive for *B. parapertussis* together and that infected symptomatic patients reported "prior exposure to pertussis," suggests that it might be beneficial to formally adopt a similar strategy for *B. parapertussis*.

The findings of several studies suggest that *B. parapertussis* may be increasing in the US and globally; besides the *B. parapertussis* outbreak described here, increased detection and other *B. parapertussis* outbreaks have been described.[22–28] A possible explanation for these observations may be selective pressures exerted on *Bordetella* species, especially given that current pertussis vaccines are likely ineffective against *B. parapertussis*. It is also possible that surveillance and detection have improved, through improved diagnostics, and specifically, inclusion of *B. parapertussis* in some assays used for pertussis testing of nasopharyngeal specimens.

It is important to note that all data presented in the present study are based on PCR only, without culture. While PCR provides excellent sensitivity, culture may be more definitive due to its specificity.[34] Another possible limitation of the study is that not everyone seeks medical attention for testing. In particular, it is possible that less severe parapertussis infections may have been left unidentified. It is also important to note that healthcare providers' practices of testing for *B. parapertussis* can be variable and influenced by the presence of recent positive testing. Another limitation lies in the fact that our findings are retrospective and observational. Specific to the Mayo Clinic Rochester study population, the catchment area for the Mayo Clinic is small, extending predominantly into Southeastern Minnesota. This and the small sample size limit our ability to make generalized inferences. For the Mayo Medical Laboratories data, it is important to note that certain regions of country, especially some West Coast states, and Hawaii and Alaska, are less represented than others.

In conclusion, in 2014, there was an outbreak of *B. parapertussis* in Southeastern Minnesota and likely other parts of the US. Symptoms were similar to those expected with *B. pertussis*. All patients had been vaccinated against pertussis. Results of this study demonstrate that *B. parapertussis* can cause a cough illness comparable to that caused by *B. pertussis* and that it is not prevented by pertussis vaccination.

Acknowledgments

This work was presented in part at the 55th Interscience Conference of Antimicrobial Agents and Chemotherapy, San Diego, CA, 2015.

References

[1] Rohani P, Drake J. The decline and resurgence of pertussis in the US. Epidemics 2011;3:183–8.
[2] Cherry JD. Epidemiology of pertussis. Pediatr Infect Dis J 2006;25: 361–2.
[3] Mattoo S, Cherry J. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to *Bordetella pertussis* and other *Bordetella* subspecies. Clin Microbiol Rev 2005;18:326–82.
[4] Adams DA, Jajosky RA, Ajani U, et al. Centers for Disease Control and Prevention (CDC)Summary of notifiable diseases—United States, 2012. MMWR Morb Mortal Wkly Rep 2014;61:1–21.
[5] Adams D, Fullerton K, Jajosky R, et al. Summary of notifiable infectious diseases and conditions—United States, 2013. MMWR Morb Mortal Wkly Rep 2015;62:1–22.
[6] Adams DA, Gallagher KM, Jajosky RA, et al. Summary of notifiable diseases—United States, 2011. MMWR Morb Mortal Wkly Rep 2013; 60:1–17.
[7] Centers for Disease Control and Prevention (CDC)Summary of notifiable diseases—United States, 2010. MMWR Morb Mortal Wkly Rep 2012; 59:1–11.
[8] Cherry JD, Seaton BL. Patterns of *Bordetella parapertussis* respiratory illnesses: 2008–2010. Clin Infect Dis 2012;54:534–7.
[9] Liese JG, Renner C, Stojanov S, et al. Clinical and epidemiological picture of *B. pertussis* and *B. parapertussis* infections after introduction of acellular pertussis vaccines. Arch Dis Child 2003;88:684–7.
[10] He Q, Viljanen MK, Arvilommi H, et al. Whooping cough caused by *Bordetella pertussis* and *Bordetella parapertussis* in an immunized population. JAMA 1998;280:635–7.
[11] Lavine J, Broutin H, Harvill ET, et al. Imperfect vaccine-induced immunity and whooping cough transmission to infants. Vaccine 2010; 29:11–6.
[12] David S, van Furth R, Mooi FR. Efficacies of whole cell and acellular pertussis vaccines against *Bordetella parapertussis* in a mouse model. Vaccine 2004;22:1892–8.
[13] Kurova N, Njamkepo E, Brun D, et al. Monitoring of *Bordetella* isolates circulating in Saint Petersburg, Russia between 2001 and 2009. Res Microbiol 2010;161:810–5.
[14] Gorgojo J, Harvill ET, Rodríguez ME. *Bordetella parapertussis* survives inside human macrophages in lipid raft-enriched phagosomes. Infect Immun 2014;82:5175–84.
[15] Gorgojo J, Lamberti Y, Valdez H, et al. *Bordetella parapertussis* survives the innate interaction with human neutrophils by impairing bactericidal trafficking inside the cell through a lipid raft-dependent mechanism mediated by the lipopolysaccharide O antigen. Infect Immun 2012;80: 4309–16.
[16] Zhang X, Rodríguez ME, Harvill ET. O antigen allows *B. parapertussis* to evade *B. pertussis* vaccine-induced immunity by blocking binding and functions of cross-reactive antibodies. PLoS One 2009;4: e6989.
[17] Zhang X, Goebel EM, Rodríguez ME, et al. The O antigen is a critical antigen for the development of a protective immune response to *Bordetella parapertussis*. Infect Immun 2009;77:5050–8.
[18] Wolfe DN, Goebel EM, Bjornstad ON, et al. The O antigen enables *Bordetella parapertussis* to avoid *Bordetella pertussis*-induced immunity. Infect Immun 2007;75:4972–9.
[19] Goebel EM, Wolfe DN, Elder K, et al. O antigen protects *Bordetella parapertussis* from complement. Infect Immun 2008;76:1774–80.
[20] Long GH, Karanikas AT, Harvill ET, et al. Acellular pertussis vaccination facilitates *Bordetella parapertussis* infection in a rodent model of bordetellosis. Proc Biol Sci 2010;277:2017–25.
[21] Lautrop H. Epidemics of parapertussis—20 years' observations in Denmark. Lancet 1971;297:1195–8.
[22] Spicer KB, Salamon D, Cummins C, et al. Occurrence of 3 *Bordetella* species during an outbreak of cough illness in Ohio: epidemiology, clinical features, laboratory findings and antimicrobial susceptibility. Pediatr Infect Dis J 2014;33:e162–7.
[23] Koepke R, Bartholomew ML, Eickhoff JC, et al. Widespread *Bordetella parapertussis* infections—Wisconsin, 2011–2012: clinical and epidemiologic features and antibiotic use for treatment and prevention. Clin Infect Dis 2015;61:1421–31.
[24] Javed S, Said F, Eqani SAMA, et al. *Bordetella parapertussis* outbreak in Bisham, Pakistan in 2009–2010: fallout of the 9/11 syndrome. Epidemiol Infect 2015;143:2619–23.
[25] Bokhari H, Said F, Syed MA, et al. Whooping cough in Pakistan: *Bordetella pertussis* vs *Bordetella parapertussis* in 2005–2009. Scand J Infect Dis 2011;43:818–20.
[26] Zouari A, Smaoui H, Brun D, et al. Prevalence of *Bordetella pertussis* and *Bordetella parapertussis* infections in Tunisian hospitalized infants: results of a 4-year prospective study. Diagn Microbiol Infect Dis 2012; 72:303–17.

[27] Tomialoic R, Stefanoff P, Paradowska-Stankiewicz I, et al. Incidence and factors predicting whooping cough due to parapertussis diagnosis among patients referred to general practitioners, Poland, 2009–2011. Eur J Clin Microbiol Infect Dis 2015;34:101–7.
[28] Watanabe M, Nagai M. Whooping cough due to *Bordetella parapertussis*: an unresolved problem. Expert Rev Anti Infect Ther 2004; 2:447–54.
[29] Sloan L, Hopkins MK, Mitchell PS, et al. Multiplex LightCycler PCR assay for detection and differentiation of *Bordetella pertussis* and *Bordetella parapertussis* in nasopharyngeal specimens. J Clin Microbiol 2002;40:96–100.
[30] Bottero D, Gaillard ME, Errea A, et al. Outer membrane vesicles derived from *Bordetella parapertussis* as an acellular vaccine against *Bordetella parapertussis* and *Bordetella pertussis* infection. Vaccine 2013;31: 5262–8.
[31] Rumbo M, Hozbor D. Development of improved pertussis vaccine. Hum Vaccin Immunother 2014;10:2450–3.
[32] Theofiles AG, Cunningham SA, Chia N, et al. Pertussis outbreak, Southeastern Minnesota, 2012. Mayo Clin Proc 2014;89:1378–88.
[33] Domínguez A, Godoy P, Toledo D, et al. Importance of enhanced surveillance for prevention of pertussis in children. Pediatr Infect Dis J 2015;34:729–33.
[34] Dragsted DM, Dohn B, Madsen J, et al. Comparison of culture and PCR for detection of *Bordetella pertussis* and *Bordetella parapertussis* under routine laboratory conditions. J Med Microbiol 2004;53: 749–54.