Editorial

Pertussis: An Underappreciated Risk for Nosocomial Outbreaks

David J. Weber, MD, MPH; William A. Rutala, PhD, MPH

Between 1988 and 1996, the number of cases of pertussis reported in the United States has ranged between 2,719 and 7,796, considerably higher than levels reported between 1976 and 1980.[1] The highest attack rate of pertussis occurs in children <1 year of age, but approximately 25% of cases reported in 1996 were in persons ⩾15 years of age. Pertussis is highly contagious; secondary attack rates exceed 80% among highly susceptible household contacts.[2] Pertussis is a worldwide problem; the World Health Organization estimated that in 1994 approximately 40 million cases occurred worldwide, with 360,000 children dying.[3]

PERTUSSIS IN THE ADULT

Recent studies have shed new light on the epidemiology of pertussis in the adult.[4] Studies using serology for diagnosis have found that pertussis is a common cause of prolonged cough (ie, >2 weeks) in the adult.[5-7] Household studies have demonstrated a high attack rate in homes with infected children and that adults may serve as the index case.[8-12] In one study of 257 adult pertussis cases in 121 families, the following symptoms were reported: cough, 91%; any cough >21 days, 80%; spasmodic cough >21 days, 63%; sleep disturbed by coughing, 52%; cough followed by choking or vomiting, 53%; whoop, 8%.[12] Compared with children, the following symptoms are less common in adults: facial flushing due to cough, cough-induced vomiting, whoop, and cyanosis with cough.[8,10] Subclinical pertussis may be common in adults with household exposures.[13] Adults with mild respiratory disease have transmitted infection to children.[14] Studies of pertussis in adults suggest that the common belief that life-long immunity follows *Bordetella pertussis* infection is incorrect and that reinfection is common in both previously vaccinated and nonvaccinated persons.[4,9,11] Additionally, studies in adults have demonstrated that culture alone is insensitive for the diagnosis of pertussis.[5,10,15]

Adolescents and young adults play an important role in the transmission of pertussis, because immunization-induced immunity to pertussis wanes with increasing age and disease in adults frequently is not diagnosed or treated because it is often mild or atypical.[16,17]

PERTUSSIS IN HEALTHCARE FACILITIES

In this issue, Haiduven and colleagues report that their institution had 49 pertussis exposures over a 9-year period from 1989 to 1997.[18] Our experience is similar: 40 employees were exposed to 15 patients with pertussis from 1994 to 1997.

Multiple outbreaks of pertussis in healthcare facilities have been reported in the literature.[15,19-24] The median number of patients with pertussis was 38 (range, 2-107); of symptomatic staff, 5 (range, 4-41); and of infected staff, 7 (range, 5-42). However, during one large community outbreak, pertussis occurred in 87 employees.[25] These outbreaks have resulted from failure to recognize and isolate infected infants and children, failure to recognize and treat disease in staff members, and failure to institute control measures rapidly. A cohort study of healthcare workers in which pertussis serology was determined every 6 months demonstrated frequent pertussis infection.[26] The Centers for Disease Control and Prevention (CDC)[27] and infectious disease experts[28,29] recommend the following guidelines for managing pertussis exposures: (1) isolate suspected or known infected patients using Droplet Precautions; (2) provide postexposure prophylaxis for all asymptomatic

From the Division of Infectious Disease, University of North Carolina School of Medicine and the Departments of Hospital Epidemiology and Occupational Health, University of North Carolina Hospitals, Chapel Hill, North Carolina.

Address reprint requests to David J. Weber, MD, MPH, 547 Burnett-Womack, CB #7030, Division of Infectious Diseases, UNC at Chapel Hill, Chapel Hill, NC 27599-7030.

98-ED-132. Weber DJ, Rutala WA. Pertussis: an underappreciated risk for nosocomial outbreaks. Infect Control Hosp Epidemiol *1998;19:825-828.*

exposed employees; (3) evaluate all symptomatic employees for pertussis, and provide appropriate therapy; and (4) furlough symptomatic employees during the first 5 days of their therapy. Haiduven and colleagues have provided a valuable guide for infection control professionals by publishing their detailed protocols for managing pertussis exposures. In addition to following CDC guidelines, Haiduven and coworkers have instituted the following interventions: (1) exposed asymptomatic healthcare workers are required to wear a mask whenever caring for a child under the age of 4 years, until 5 days of chemoprophylaxis have been completed, and (2) exposed healthcare workers who refuse prophylaxis must mask from 7 days after the first possible date of exposure until 14 days after the last possible date of exposure to a case of pertussis. As the authors note, this approach is more conservative than that recommended by the CDC. Haiduven and associates recommend the following antibiotics (in order of preference): erythromycin 500 mg qid for 14 days, clarithromycin 500 mg bid for 14 days, azithromycin (no dose or duration listed), oxytetracycline 500 mg qid for 14 days, or trimethoprim-sulfamethoxazole 1 DS bid for 14 days. Because erythromycin at this dose and duration frequently causes gastrointestinal irritation, we preferentially use clarithromycin or azithromycin. Although oxytetracycline has in the past proved successful in treating pertussis, in vitro studies suggest only modest to good activity.[30,31] In accordance with recommendations published in the *Red Book,*[32] the primary alternative for macrolide-intolerant healthcare workers is trimethoprim-sulfamethoxazole.

PROBLEMS WITH IMPLEMENTING INFECTION CONTROL POLICIES TO CONTROL PERTUSSIS

There are several important problems with implementing policies to minimize nosocomial transmission of pertussis. First, many physicians are not familiar with the manifestations of pertussis, especially in adults. Hence, the diagnosis frequently is missed, leading to failure to institute proper isolation and therapy. Second, currently available tests such as direct fluorescent antibody and culture lack sensitivity and specificity and are rarely positive in adults who have been symptomatic for more than 2 weeks. Detection of antibody using acute and convalescent sera is an important research tool but has little applicability for rapid detection and therapy. Third, currently available pertussis vaccines are not recommended for persons aged $\geq$7 years.[33] Fourth, erythromycin, the only drug currently approved by the Food and Drug Administration (FDA) for pertussis, requires qid dosing for 2 weeks. Gastrointestinal toxicity frequently limits its use in healthcare workers. Fifth, only limited data are available on the rates of acquisition of pertussis by healthcare personnel, risks of transmission, and success of currently recommended infection control measures.

RECENT ADVANCES

Fortunately, several areas of recent research may allow improved prevention and management of nosocomial pertussis. Educating pediatricians, internists, and healthcare workers regarding the resurgence of pertussis and the recognition of pertussis in adults is being accomplished by recent editorials[34] and reviews.[35,36] Methods for educating healthcare workers have been described.[25] The forms produced by Haiduven and colleagues are likely to be very useful in the education of healthcare workers regarding the detection and management of patients with pertussis.

Erythromycin is the only drug approved by the FDA for the treatment of pertussis; the estolate form is preferred by some clinicians because of superior pharmacokinetics. *B pertussis* is highly susceptible in vitro to erythromycin.[37,38] Erythromycin has been shown to decrease the duration of illness when administered early in the course of pertussis and to eliminate *B pertussis* from the nasopharynx. For these reasons, erythromycin is considered the drug of choice for the treatment and prophylaxis of pertussis.[16,28] Erythromycin therapy of infected persons plus chemoprophylaxis of exposed persons has been used successfully to reduce secondary spread in households[39,40] or to terminate outbreaks in healthcare institutions.[15,41] The potential epidemiological flaws in clinical trials of erythromycin prophylaxis have been reviewed.[42] Of concern, erythromycin-resistant isolates of *B pertussis* have been isolated occasionally from clinical specimens in the United States.[43,44] *B pertussis* is also susceptible in vitro to trimethoprim-sulfamethoxazole,[38] the newer macrolides azithromycin and clarithromycin,[37] and the quinolones levofloxacin, ciprofloxacin, and ofloxacin.[45] Trimethoprim- sulfamethoxazole has been demonstrated to be effective therapy in small clinical trials[46] and therefore is the recommended alternative for treatment or chemoprophylaxis of individuals intolerant to erythromycin.[28,45] However, its efficacy as a chemoprophylactic agent has not been evaluated. Small clinical trials suggest that clarithromycin and azithromycin also are effective for the treatment of pertussis.[47] Although older studies had suggested that a 14-day course of erythromycin therapy was required for eradication of *B pertussis,* recent trials have suggested that the following shorter courses of antibiotics are as successful as the standard 14-day course of erythromycin: 7 days of erythromycin estolate (40 mg/kg/d; maximum dose 1 g),[48] 7 days of clarithromycin,[47] or 5 days of azithromycin.[47] Because of the high frequency of gastrointestinal intolerance with erythromycin, we—like Haiduven and colleagues—have switched to one of the newer macrolides.

DTaP vaccine (diphtheria, tetanus toxoid, acellular pertussis) is now approved for all pediatric age groups. Studies have shown acellular pertussis vaccine to be safer and at least as effective as whole-cell vaccine.[49,50] The DTaP vaccines will need to be reformulated for use in

adults, because all infant formulations contain more diphtheria toxoid than is recommended for persons aged ⩾7 years.[49] Small clinical trials suggest that acellular pertussis vaccine elicits a good antibody response and is safe when provided to adults.[51,52] Acellular pertussis vaccine has be used to aid in containing nosocomial outbreaks.[41] Large-scale trials in adults are underway. Introduction of booster immunizations for adults has been recommended if ongoing trials demonstrate the acellular vaccine to be safe and effective in adults.[53]

New diagnostic tests are being used now to study the epidemiology of pertussis.[54] The polymerase chain reaction (PCR) is sensitive and specific,[55,56] but if introduced into clinical use will require increased technician time.[57] PCR has been used to document nosocomial acquisition of pertussis.[58] In erythromycin-treated subjects, PCR has been shown to demonstrate *B pertussis* after cultures turned negative.[59] It is likely that, in the next decade, the diagnosis of pertussis will be made by using a combination of methods including direct fluorescent antibody, culture, PCR, and serology; the exact tests chosen will depend on the patient population, treatment status, and duration of symptoms.[54]

RESEARCH NEEDS

Future research should be undertaken to establish the risk of nosocomial acquisition of pertussis. The efficacy of the new macrolides, especially when used in short courses as postexposure prophylaxis, should be studied, because they would be tolerated much better than erythromycin. If acellular pertussis vaccine is demonstrated to be safe and effective in adults, additional studies should be undertaken to evaluate its efficacy in preventing nosocomial acquisition of pertussis by healthcare workers. Finally, improved diagnostic methods that have enhanced sensitivity and specificity without undue costs need to be validated and become commercially available for use by clinical microbiology laboratories.

REFERENCES

1. Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 1996. *MMWR* 1996;45(53):10, 46-47.
2. Mortimer EA. Pertussis and its prevention: a family affair. *J Infect Dis* 1990;161:473-479.
3. Ivanoff B, Robertson SE. Pertussis: a worldwide problem. *Dev Biol Stand* 1997;89:3-13.
4. Cherry JD. The role of *Bordetella pertussis* infections in adults in the epidemiology of pertussis. *Dev Biol Stand* 1997;89:181-186.
5. Mink CM, Cherry JD, Christenson P, Lewis K, Pineda E, Shilan D, et al. A search for *Bordetella pertussis* infection in university students. *Clin Infect Dis* 1992;14:464-471.
6. Jansen DL, Gray GC, Putnam SD, Lynn F, Meade BD. Evaluation of pertussis in US Marine Corps trainees. *Clin Infect Dis* 1997;25:1099-1107.
7. Nenning ME. Shinefield HR, Edwards KM, Black SB, Fireman BH. Prevalence and incidence of adult pertussis in an urban population. *JAMA* 1996;275:1672-1674.
8. Aoyama T, Takeuchi Y, Groto A, Iwai H, Murase Y, Iwata T. Pertussis in adults. *American Journal of Diseases in Children* 1992;146:163-166.
9. Schmitt-Grohe S, Cherry JD, Heininger U, Uberall MA, Pineda E, Stehr K. Pertussis in German adults. *Clin Infect Dis* 1995;21:860-866.
10. Wirsing von Konig CH, Postels-Multani S, Bock HL, Schmitt HJ. Pertussis in adults: frequency of transmission after household exposure. *Lancet* 1995;346:1326-1329.
11. Deen JL, Mink CM, Cherry JD, Christenson PD, Pineda EF, Lewis K, et al. Household contact study of *Bordetella pertussis* infections. *Clin Infect Dis* 1995;21:1211-1219.
12. Postels-Multani S, Schmitt HJ, Wirsing von Konig CH, Bock HL, Bogaerts H. Symptoms and complications of pertussis in adults. *Infection* 1995;23:139-142.
13. Long SS, Welkon CJ, Clark JL. Widespread silent transmission of pertussis in families: antibody correlates of infection and symptomatology. *J Infect Dis* 1990;161:480-486.
14. Christie CDC, Baltimore RS. Pertussis in neonates. *American Journal of Diseases in Children* 1989;143:1199-1202.
15. Steketee RW, Burstyn DG, Wassilak SG, Adkins WN Jr, Polyak MB, Davis JP, et al. A comparison of laboratory and clinical methods for diagnosing pertussis in an outbreak in a facility for the developmentally disabled. *J Infect Dis* 1988;157:441-449.
16. Hoppe JE. Update on epidemiology, diagnosis, and treatment of pertussis. *Eur J Clin Microbiol Infect Dis* 1996;15:189-193.
17. Black S. Epidemiology of pertussis. *Pediatr Infect Dis J* 1997;16:S85-S89.
18. Haiduven DJ, Hench CP, Simpkins SM, Stevens DA. Standardized management of patients and employees exposed to pertussis. *Infect Control Hosp Epidemiol* 1998;19:861-864.
19. Kurt TL, Yeager AS, Guenette S, Dunlop S. Spread of pertussis by hospital staff. *JAMA* 1972;221:264-267.
20. Linnemann CC Jr, Ramundo N, Perlstein PH, Minton SD, Englender GS. Use of pertussis vaccine in an epidemic involving hospital staff. *Lancet* 1975;2:540-543.
21. Valenti WM, Pincus PH, Messner MK. Nosocomial pertussis: possible spread by a hospital visitor. *American Journal of Diseases in Children* 1980;134:520-521.
22. Fisher MC, Long SS, McGowan KL, Kaselis E, Smith DG. Outbreak of pertussis in a residential facility for handicapped people. *J Pediatr* 1989;114:934-939.
23. Addiss DG, Davis JP, Meade BD, Burstyn DG, Melssner M, Zastrow JA, et al. A pertussis outbreak in a Wisconsin nursing home. *J Infect Dis* 1991;164:704-710.
24. Tanaka Y, Fujinaga K, Goto A, Iwai H, Aoyama T, Murase Y, et al. Outbreak of pertussis in a residential facility for handicapped people. *Dev Biol Standard* 1991;73:329-332.
25. Christie CD, Glover AM, Wilke MJ, Marx ML, Reising SF, Hutchinson NM. Containment of pertussis in the regional pediatric hospital during the greater Cincinnati epidemic of 1993. *Infect Control Hosp Epidemiol* 1995;16:556-563.
26. Deville JG, Cherry JD, Christenson PD, Pineda E, Leach CT, Kuhis TL, et al. Frequency of unrecognized *Bordetella pertussis* infections in adults. *Clin Infect Dis* 1995;21:639-642.
27. Bolyard EA, Tablan OC, Williams WW, Pearson ML, Shapiro CN, Deitchman SD, et al. Guideline for infection control in health care personnel, 1998. *Am J Infect Control* 1998;26:289-354.
28. Rutala WA, Weber DJ. Management of healthcare workers exposed to pertussis. *Infect Control Hosp Epidemiol* 1994;15:411-415.
29. Strebel P. Pertussis. In: APIC Infection Control and Applied Epidemiology. *Principles and Practice.* St Louis, MO: Mosby; 1996:71.1-71.5.
30. Bass JW, Crast FW, Kotheimer JB, Mitchell IA. Susceptibility of *Bordetella pertussis* to nine antimicrobial agents. *American Journal of Diseases in Children* 1969;117:276-280.
31. Hoppe JE, Haug A. Antimicrobial susceptibility of *Bordetella pertussis,* part I: infection 1988;16:126-130.
32. American Academy of Pediatrics. Pertussis In: Peter G, ed. *1997 Red Book: Report of the Committee on Infectious Diseases.* 24th ed. Elk Grove Village, IL: American Academy of Pediatrics 1997:394-407.
33. Centers for Disease Control and Prevention. Pertussis vaccination: use of acellular pertussis vaccines among infants and young children—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997;46(RR-7):1-23.
34. Cherry JD. Nosocomial pertussis in the nineties. *Infect Control Hosp Epidemiol* 1995;16:553-555.
35. Mortimer EA Jr. Pertussis and pertussis vaccine. *Adv Ped Infect Dis* 1990;5:1-33.
36. Waggoner-Fountain L, Hayden GF. Pertussis in primary care practice. Recent advances in diagnosis, treatment, and prevention. *Prim Care* 1996;23:793-804.
37. Hoppe JE, Bryskier A. In vitro susceptibilities of *Bordetella pertussis* and *Bordetella parapertussis* to two ketolides (HMR 3004 and HMR 3647), four macrolides (azithromycin, clarithromycin, erythromycin A, and roxithromycin), and two ansamycins (rifampin and rifapentine). *Antimicrob Agents Chemother* 1998;42:965-966.
38. Brett M, Short P, Beatson S. The comparative in-vitro activity of roxithromycin and other antibiotics against *Bordetella pertussis. J Antimicrob Chem* 1998;41(suppl B):23-27.
39. Sprauer MA, Cochi SL, Zell ER, Sutter RW, Mullen JR, Englender SJ, et al. Prevention of secondary transmission of pertussis in households with early use of erythromycin. *American Journal of Diseases in Children* 1992;146:177-181.
40. De Serres G, Boulianne N, Duval B. Field effectiveness of erythromycin prophylaxis to prevent pertussis within families. *Pediatr Infect Dis J* 1995;14:969-975.

41. Shefer A, Dales L, Nelson M, Werner B, Baron R, Jackson R. Use and safety of acellular pertussis vaccine among adult hospital staff during an outbreak of pertussis. *J Infect Dis* 1995;171:1053-1056.
42. Dodhia H, Miller E. Review of the evidence for the use of erythromycin in the management of persons exposed to pertussis. *Epidemiol Infect* 1998;120:143-149.
43. Lewis K, Saubolle MA, Tenover FC, Rudinsky MF, Barbour SD, Cherry JD. Pertussis caused by an erythromycin-resistant strain of *Bordetella pertussis. Pediatr Infect Dis J* 1995;14:388-391.
44. Korgenski EK, Daly JA. Surveillance and detection of erythromycin resistance in *Bordetella pertussis* isolates recovered from a pediatric population in the Intermountain West region of the United States. *J Clin Microbiol* 1997;35:2989-2991.
45. Hoppe JE, Rahimi-Galougahi E, Seibert G. In vitro susceptibilities of *Bordetella pertussis* and *Bordetella parapertussis* to four fluoroquinolones (levfloxacin, d-ofloxacin, ofloxacin, and ciprofloxacin), cefpirome, and meropenem. *Antimicrob Agents Chemother* 1996;40:807-808.
46. Hoppe JE, Halm U, Hagedorn HJ, Kraminer-Hagedorn A. Comparison of erythromycin ethylsuccinate and co-trimoxazole for treatment of pertussis. *Infection* 1989;17:227-231.
47. Aoyama T, Sunakawa K, Iwata S, Takeuchi Y, Fujii R. Efficacy of short-term treatment of pertussis with clarithromycin and azithromycin. *J Pediatr* 1996;129:761-764.
48. Halperin SA, Bortolussi R, Langley JM, Miller B, Eastwood BJ. Seven days of erythromycin estolate is as effective as fourteen days for the treatment of *Bordetella pertussis* infections. *Pediatrics* 1997;100:65-71.
49. Centers for Disease Control and Prevention. Immunization of health-care workers: recommendations to the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR* 1997;46(RR-18):1-41.
50. Pichichero ME. Acellular pertussis vaccines: towards an improved safety profile. *Drug Safety* 1996;15:311-324.
51. Edwards KM, Decker MD, Graham BS, Mezzatesta J, Scott J, Hackell J. Adult immunization with acellular pertussis vaccine. *JAMA* 1993;269:53-56.
52. Tommaso AD, Bartalini M, Peppoloni S, Podda A, Rappuoli R, De Magistris MT. Acellular pertussis vaccines containing genetically detoxified pertussis toxin induce long-lasting humoral and cellular responses in adults. *Vaccine* 1997;15:1218-1224.
53. Keitel WA, Edwards KM. Pertussis in adolescents and adults: time to reimmunize? *Semin Respir Infect* 1995;10:51-57.
54. Muller FC, Hoppe JE, von Konig CW. Laboratory diagnosis of pertussis: state of the art in 1997. *J Clin Microbiol* 1997;35:2435-2443.
55. Reizenstein E, Lindberg L, Mollby R, Hallander HO. Validation of nested *Bordetella* PCR in pertussis vaccine trial. *J Clin Microbiol* 1996;34:810-815.
56. Reizenstein E. Diagnostic polymerase chain reaction. In: Brown F, Greco D, Mastrantonio P, Salmaso S, Wassilak S. *Pertussis Vaccine Trials.* Dev Biol Stand. Basel, Karger, 1997;89:247-254.
57. Erlandsson A, Backman A, Tornqvist E, Olsen P. PCR assay or culture for diagnosis of *Bordetella pertussis* in the routine diagnostic laboratory? *J Infect* 1997;35:221-224.
58. Matlow AG, Nelson S, Wray R, Cox P. Nosocomial acquisition of pertussis diagnosed by polymerase chain reaction. *Infect Control Hosp Epidemiol* 1997;18:715-716.
59. Edelman K, Nikkari S, Ruuskanen O, He Q, Viljanen M, Mertsola J. Detection of *Bordetella pertussis* by polymerase chain reaction and culture in the nasopharynx of erythromycin-treated infants with pertussis. *Pediatr Infect Dis J* 1996;15:54-57.