Published in final edited form as:

Pediatr Crit Care Med. 2011 July ; 12(4): 387–392. doi:10.1097/PCC.0b013e3181fe4058.

The Collaborative Pediatric Critical Care Research Network (CPCCRN) Critical Pertussis Study: Collaborative Research in Pediatric Critical Care Medicine

Jeri S. Burr, MS, RN-BC, CCRC¹, Tammara L. Jenkins, MSN, RN, CCRN², Rick Harrison, MD, FAAP³, Kathleen Meert, MD, FCCM⁴, K.J.S. Anand, MBBS, D.Phil., FAAP, FCCM, FRCPCH⁵, John T. Berger, MD, FACC, FCCM⁶, Jerry Zimmerman, MD, PhD, FCCM⁷, Joseph Carcillo, MD⁸, J. Michael Dean, MD, MBA, FCCM, FCCP, FAAP¹, Christopher J. L. Newth, MD ChB, FRCPCH⁹, Douglas F. Willson, MD¹⁰, Ronald C. Sanders Jr, MD, MS, FAAP¹¹, Murray M. Pollack, MD, FCCM, FAAP¹², Eric Harvill, PhD¹³, and Carol E. Nicholson, MD, MS, FAAP² for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCCRN)

¹University of Utah, Salt Lake City, UT, USA

²*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Dept. of Health and Human Services, Bethesda, MD, USA

³Mattel Children's Hospital UCLA, Los Angeles, CA, USA

⁴Children's Hospital of Michigan, Detroit, MI, USA

⁵University of Tennessee Health Science Center, Memphis, TN, USA

⁶Children's National Medical Center, Washington, DC, USA

⁷Seattle Children's Hospital, Seattle, WA, USA

⁸Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

⁹Children's Hospital of Los Angeles, Los Angeles, CA, USA

¹⁰University of Virginia Children's Hospital, Charlottesville, VA, USA

¹¹Children's Hospital of Arkansas, Little Rock, AR, USA

¹²Phoenix Children's Hospital, Phoenix, AZ, USA

¹³The Pennsylvania State University, University Park, PA, USA

Abstract

Objective—To provide an updated overview of critical pertussis to the pediatric critical care community and describe a study of critical pertussis recently undertaken.

Setting—The six sites, seven hospitals of the Collaborative Pediatric Critical Care Research Network and 17 outside sites at academic medical centers with PICUs.

Corresponding Author: Jeri S. Burr, Program Director/Data Coordinating Center/University of Utah, Collaborative Pediatric Critical Care Research Network, 295 Chipeta Way, PO Box 581289, Salt Lake City, Utah, 841580-1289, Phone: (801) 587-7753 Fax: (801) 587-7761, jeri.burr@hsc.utah.edu.

Conflict of interest: All authors, no conflict reported

Disclaimer: The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Results—Despite high coverage for childhood vaccination, pertussis causes substantial morbidity and mortality in United States children, especially among infants. In pediatric intensive care units, *Bordetella pertussis* is a community-acquired pathogen associated with critical illness and death. The incidence of medical and developmental sequelae in critical pertussis survivors remains unknown, and the appropriate strategies for treatment and support remain unclear. The CPCCRN Critical Pertussis Study has begun to evaluate critical pertussis in a prospective cohort.

Conclusion—Research is urgently needed to provide an evidence base that might optimize management for critical pertussis, a serious, disabling, and too often fatal illness for United States children, and those in the developing world.

Keywords

pertussis; respiratory failure; study design; outcomes; multiple organ system failure; advanced life support

BACKGROUND

Pertussis, also known as whooping cough, is a highly contagious acute respiratory illness caused by the gram-negative bacterial pathogen, *Bordetella pertussis* (1). Children may present with a paroxysmal cough, posttussive vomiting, an inspiratory whoop and duration of cough lasting 1–3 months (2). Clinical presentation of pertussis is thought to be influenced by a number of factors including age, immunocompetence and acquired immunity. Coughing episodes caused by pertussis in infants and their management require skilled and meticulous nursing and medical care.

There is a distinction between classic pertussis and *critical pertussis* as described in the series reported by Halperin and others (3–5). Common reasons for hospitalization due to pertussis are apnea (with or without cough paroxysms), pneumonia, and seizures (6, 7). Pertussis illness requiring admission to the pediatric intensive care unit (PICU) is *critical pertussis* and defined as such in this report (7–9).

Although substantial morbidity is recognized in other age groups, most hospitalizations and nearly all deaths from critical pertussis are reported in infants aged <6 months (10). Death or disability following pertussis illness is probably more common than generally recognized (7). The young infants who constitute the majority of cohorts with critical pertussis illness present special diagnostic and therapeutic challenges in sepsis and organ failure (8). Moreover, pathogenesis of organ failure in critically ill infants is complex and incompletely understood; specific host susceptibility and phenotypes interactions among *B. pertussis* strains are implicated (1, 11, 12).

The objectives of this review are to provide an overview of current knowledge about the problem, and to describe a national study of critical pertussis presently underway.

SIGNIFICANCE AND CHARACTERISTICS OF CRITICAL PERTUSSIS

In recent years, reported pertussis cases in the United States have increased from a historic low of 1,010 in 1976, following widespread immunizations in the 1950s, to a peak of 25,857 cases in 2004, despite high immunization coverage rates for childhood pertussis (10, 13, 14). During 2000–2008, a total of 127,672 cases of pertussis were reported to the Centers for Disease Control and Prevention's (CDC) National Notifiable Diseases Surveillance System (15). Resurgence of pertussis in the last 20 years is evident in Figure 1, from the Centers for Disease Control (CDC) (15). Immunity after vaccination has limited duration, and studies

show that natural immunity after pertussis infection is not much longer than that achieved by immunization (16).

Infants become infected before they are old enough either to respond to immunization or to mount an adequate response to the organism and may present already critically ill. Clinical symptoms may be atypical, and diagnosis difficult. Those with critical pertussis illness may not uniformly have a paroxysmal cough, nor exhibit an inspiratory “whoop.” Rather, recurrent episodes of autonomic instability (apnea, cyanosis, and bradycardia) may dominate the clinical picture (17, 18). It has been suggested that apnea be added to the clinical definition of critical pertussis, which is further characterized by the development of pneumonia that rapidly evolves to respiratory failure requiring mechanical support or extracorporeal membrane oxygenation.(19)

Initially, the etiology of the critical illness may be unclear. Infants admitted to the PICU may be presumptively diagnosed with sepsis and later found to have pertussis. Most will have elevated white blood cell counts, and marked lymphocytosis. Some are subsequently found to have co-infections with other viral (respiratory syncytial virus [RSV], influenza, adenovirus, others) and bacterial pathogens (20). One review of 72 children admitted with pertussis to a New Zealand PICU from 1991 to 2003 reported apnea as the leading reason for PICU admission (82%). Bradycardia (63%), pneumonia (28%) and hemoglobin desaturation (24%) as components of respiratory failure were also reported (7). It is likely that PICU admission criteria have evolved in recent years toward including only children with evidence of autonomic instability in pertussis illness; thus, cohort analysis over the 12 year span in the New Zealand report may be difficult to interpret in present critical care practice.

In a retrospective 1999 Canadian study of 48 infants hospitalized for pertussis over an 11-year period, Halperin *et al* reported that 16 (33%) died (21). Although the study was retrospective and underpowered for statistical significance, various observations of interest were reported. Thirteen of the 16 fatalities occurred in females; greater female mortality is reported in other series (2). This observation at first glance seems counter-intuitive to those accustomed to providing pediatric intensive care; the etiology of the differential mortality in females remains unclear (22). Eight of these children had post-mortem examination; all showed evidence of alveolar hemorrhage and pneumonitis, consistent with pulmonary hypertension resulting from veno-occlusive disease (19, 23, 24). Evidence of anoxic heart damage was present in half of those examined, and other findings of multiple organ system failure were found in several. Positive culture evidence of infection with other pathogens was reported in half of this post mortem series.

Differential diagnosis of pertussis is presented and taught in pediatric education and training, although distinguishing features are variable (25, 26). Respiratory failure with accompanying multiple organ system failure occurs in some children, and advanced life support is required (27). The exact relationship of length of symptoms to cardiopulmonary instability and the evolution of the course of pertussis critical illness is not described in detail in larger cohorts.

DISEASE BURDEN OF CRITICAL PERTUSSIS

Critical pertussis causes substantial morbidity and mortality for children in the United States, even though immunization coverage rates are high. During the 1990s, the mean annual incidence of pertussis among infants <4 months old increased to 88.7 per 100,000 population from 63.4 per 100,000 population in the 1980s (28). During 1990–1999 there were 84 pertussis-related known deaths among infants <4 months increasing to 111 in the same age group during 2000–2008. There were 289 pertussis-related deaths reported to CDC

from 1999–2008 (Table 1); infants aged <12 months accounted for 267 (92%) of fatal outcomes during that period (15). Longer term outcomes for critical pertussis survivors have not been formally studied. Indeed, the incidence of temporary or permanent disability in survivors remains unknown.

Mortality

Mortality in most pediatric critical illness diagnostic groups has fallen dramatically in the United States, but it has not decreased to the same extent for critical pertussis (8). A recently published study summarized experience with infants admitted with pertussis to an Australian PICU over a 20-year period (6). The investigators reported that infants dying of pertussis suffered from severe pneumonia, circulatory failure, encephalopathy, and multiple organ system failure. Six of seven infants needing circulatory support died (including all four treated with extracorporeal membrane oxygenation), and all deaths (n=7) occurred in infants who had pneumonia at presentation. Despite advances in life support and the treatment of organ failure in childhood critical illness, critical pertussis remains difficult to treat. Mortality in infants persists despite ventilation, nitric oxide, inotropic agents and ECMO (7). Typically, the course of critical pertussis is characterized by decreasing oxygenation and ventilation, often with evidence of significant pulmonary hypertension (3, 20, 29). Treatment with ECMO has been instituted as a temporizing measure in critical pertussis where other methodologies of advanced life support are inadequate. ECMO was used for the first time to treat critical pertussis in 1990. Since then, a total of 61 children (age range: 1 day – 2.7 years) with critical pertussis have been registered in the Extracorporeal Life Support Organization database (30). Overall mortality was greater than 70%, and significantly higher for infants who were younger than 6 weeks (84%) compared with those who were older.

Exchange transfusion and leukopheresis have been reported effective in small cohorts for correcting the pulmonary hypertension that characterizes critical pertussis, and facilitating oxygenation. Removal of abnormal leukocytes in the pulmonary vasculature is reported to be of benefit, and pulmonary vasodilators such as inhaled nitric oxide and sildenafil have also been utilized with some reported success (29, 31).

Morbidity

Overall mortality in United States PICUs has decreased to about 1.5 – 8% (8). Understanding longer term consequences (morbidity and disabilities) in survivors of pediatric critical illness and injury are research goals for pediatric critical care investigators. Children admitted to the PICU are at overall risk for adverse outcomes following hospital discharge. One study among 1,032 persons (aged 0–29 years, median age 19 months), admitted to an Australian PICU for any reason, reported that 7% of survivors died in the first two years following discharge, and 10% of survivors of PICU admission were likely to require dependent care (32). Developmental and cardiopulmonary sequelae may be common in critical pertussis survivors, but remains undescribed. Sequelae might be triggered by one of the several toxins present in *B. pertussis* infection and/or untoward effects of therapeutic interventions. For example, ECMO, invasive vascular access and monitoring, right heart catheterization, and pressor agents for hemodynamic support are reported to increase morbidity risk in survivors (33, 34).

Hospitalization in technologically advanced PICUs might be expected to escalate costs substantially (35–38). Specific health and economic effects of critical pertussis on infants, their families and society are understudied as well. Other costs such as pain and suffering, family stress, and the long-term productivity impact of caregivers of children with permanent sequelae, are likely incalculable (39, 40).

Pertussis outbreaks result in substantial costs to hospitals and health care systems even when case numbers are low. Diagnosis is often delayed or missed increasing the likelihood of transmission and the numbers of exposures. Reported pertussis outbreak costs to hospitals range from \$68,130 to \$195,342 in direct containment costs (personnel time, laboratory and medication), and from \$11,200 to \$68,015 in indirect costs (from hospital staff furlough or absenteeism) (41, 42).

INFECTION CONTROL CHALLENGES IN THE PICU

Beyond tending to the complex physiologic needs of the child at risk for evolving multisystem organ failure, there are central responsibilities in disease control in the PICU. Availability of appropriate isolation rooms may be minimal during seasons with a high incidence of infectious respiratory diseases such as RSV. The diagnostic conundrum of critical pertussis means that children with critical illness of unclear or evolving etiology may have numerous tests, as well as clinic, urgent care, and emergency department visits that expose large numbers of healthcare providers and visitors before critical pertussis is suspected and confirmed.

The American Academy of Pediatrics Red Book, CDC and the Healthcare Infection Control Practices Advisory Committee each make specific recommendations for infection control in the inpatient setting (43–46). These are summarized here as follows: (1) a child with confirmed pertussis should be in a private room or may share a room with another child with confirmed pertussis until at least 5 days of a full antimicrobial therapy course have been completed (or 21 days after cough onset if unable to take the antimicrobial therapy); (2) children with suspected pertussis, should be in a private room until pertussis is confirmed and other respiratory pathogens excluded, and then may be cohorted with another pertussis patient; (3) surgical masks, gowns and gloves should be worn when entering the room of a child with confirmed or suspected pertussis, and standard precaution guidelines for control of droplet mediated transmission followed. Additional means of infection control include limitation of patient movement or transport, precautions to prevent transmission when transport is essential and exclusion of all visitors/family members with symptoms of respiratory infection (43, 44, 46, 47). Critical pertussis cases in any individual PICU occur with relatively low frequency, and the diagnosis may not be considered during acute stabilization. Staff and family may be extensively exposed prior to diagnosis (44, 46, 48, 49).

CHEMOPROPHYLAXIS FOR EXPOSURES

Control of nosocomial pertussis is costly and disruptive. Symptomatic health care workers (especially those with a cough illness) are treated with antimicrobials and on leave from work until completion of five days of therapy. For those who either cannot or refuse to receive antimicrobial therapy, exclusion from work for 21 days from the time of cough onset is recommended (43, 44, 46). Health care personnel (HCP) in hospitals or ambulatory settings who have direct patient contact should receive a single dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) if they have not previously received Tdap (50). The impact of pertussis on productivity can be significant particularly in PICUs already dealing with manpower shortages on a chronic basis.

Theoretically, prophylactic antimicrobial treatment is not required for asymptomatic health care personnel who appropriately follow infection control guidelines. In practice, rapid control of potential and actual institutional outbreaks has followed simultaneous implementation of widespread chemoprophylaxis of all nosocomial exposures. For this reason, macrolide prophylaxis is recommended broadly to all *potentially exposed* individuals and health care personnel. First-line antimicrobial agents for pertussis treatment

and post exposure prophylaxis include erythromycin, azithromycin or clarithromycin for individuals 6 months of age or older. For children less than 6 months of age, the risk versus benefit ratio of each agent is considered. Erythromycin has been associated with the development of infantile hypertrophic pyloric stenosis (IHPS), and while neither azithromycin nor clarithromycin have been approved by the US Food and Drug Administration for infants <6 months of age, azithromycin may be the preferred macrolide for this age group because of the risk of IHPS (43, 44, 46, 51). Trimethoprim-sulfamethoxazole is an alternative for individuals unable to tolerate macrolides although not appropriate for the very young (44).

THE CPCCRN CRITICAL PERTUSSIS STUDY

In June 2008, the Collaborative Pediatric Critical Care Research Network (CPCCRN) began enrolling subjects in a descriptive, prospective cohort study of critical pertussis. Specific aims are to characterize the acute course of pertussis critical illness admission, assess health and demographic characteristics of the children who develop critical pertussis, and to assess health status and family impact following PICU discharge via assessment of developmental sequelae, and quality of life in survivors. Support is provided from the National Vaccine Program Office in the Office of the Secretary, Department of Health and Human Services, as well as the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health.

The study is a trans-Federal project: a co-investigator at the CDC provides collaboration with the laboratory, epidemiology and public health expertise available at CDC, and a basic scientist (Eric Harvill), supported by the National Institute of General Medical Sciences, is utilizing the scientific opportunity afforded by the study to elucidate *B. pertussis* pathogenesis as a factor of microbial ecology and adaptive characteristics. CPCCRN investigators plan to enroll 200 children with critical pertussis at the 7 CPCCRN sites across the United States. To date, 84 children have been enrolled, over a period of 2 years. Currently, there are about 17,000 annual PICU admissions at 7 CPCCRN sites where surveillance for critical pertussis is ongoing. In addition, investigators and staff at 17 outside sites at academic medical centers with PICUs have been recruited and trained to complete the study within 2 years. With the addition of the outside sites, nearly 33,000 annual PICU admissions are being screened for critical pertussis illness.

Developmental sequelae and quality of life will be assessed in infants who were < 12 months gestational age at PICU admission. That is, children who were premature with a gestational age <40 weeks at enrollment, are included in developmental evaluation if they were enrolled at any time prior to being 12 months old after accounting for their gestational age at birth. Investigators are seeking evidence suggestive of association patterns linking characteristics of the critical illness (support required, evidence of organ failure) to longer term outcomes in survivors.

Laboratory testing for *B. pertussis* at the CPCCRN sites will facilitate future hypothesis formation. *B. pertussis* isolates will be collected and shipped to a research laboratory that is conducting research in strain genetics. Researchers hope to identify the types of *B. pertussis* that causes lethal disease in United States infants and children.

There are several lines of evidence suggesting that groups of organisms with different and characteristic dynamics may reflect independent epidemiology of pertussis infections in various child populations (52). For example, it is possible that the seasonal peak in the incidence of *B. pertussis* in infants (hospitalized and not hospitalized) precedes the seasonal peak in adolescents. This might indicate that seasonal epidemics in adolescents are probably not the main source infecting infants. Parents with pertussis, including new mothers, are the

identified source of *B. pertussis* infection in about 25% of cases in early infancy, when rates for complications and fatalities are highest (53–55). The ability to distinguish the strains that cause severe disease in infants from other strains circulating in various populations will enable more exact understanding of the likely source of the infections.

The laboratory will use the Golden Gate platform to definitively characterize each isolate obtained from the study subjects by SNP (single nucleotide polymorphism) type. The SNP types identified will be related to those present worldwide and to that present in other age groups in survey populations in Massachusetts. These studies will address pressing questions: Is there a subset of strains that are most dangerous to young infants? Are these the same strains that cause the strong cyclical epidemics in adolescents, or the strains that percolate at lower levels in vaccinated children or in adults or elderly? The finding that a subset of *B. pertussis* lineages is associated with severe disease in infants will inform epidemiologic and therapeutic interventions and generate hypothesis-driven research.

The NICHD CPCCRN sites are geographically diverse, and the populations available to study are representative of the socio-demographic characteristics of children in the United States (56) (Table 2). Translational hypotheses will be generated and understanding of how organ failure might be triggered in critical illness and injury will be enhanced. Detailed studies of critical pertussis illness among children in cohorts with specific demographic description, high acuity and survivor follow-up assessment are largely absent from the literature (22).

CONCLUSION

Critical illness due to *B. pertussis* persists in the United States, as well as other developed countries, despite high immunization rates and modifications in immunization schedules. Limited data suggest that the burden of critical pertussis is substantial, and that the economic, health and developmental impacts for infants and their families may be underestimated (57). The CPCCRN Critical Pertussis Study, a trans-Federal project, has begun to evaluate critical pertussis in a prospective cohort. Detailed evidence of organ failure, level of support, disability and the burden for families is being collected, and represents a unique scientific opportunity. *B. pertussis* continues to evolve, with new strains emerging and apparently displacing those previously described (58, 59). Isolation of these strains will allow future experimental work to determine both the virulence mechanisms and immune parameters involved in control and clearance. The NICHD CPCCRN Critical Pertussis Study is a scientific opportunity to look at a relatively homogeneous cohort of children during and after critical illness, as well as to describe the pathogenesis of critical organ failure in the young. It is expected to be of benefit for United States children, as well as the 500,000 children who still die annually of critical pertussis in the global community (25). Generation of hypotheses for further clinical and basic research will be a major benefit of this work.

Acknowledgments

Members of the CPCCRN participating in this study: University of Utah (Data Coordinating Center), Salt Lake City, UT: J. Michael Dean, MD, Jeri Burr, MS, RN-BC, CCRC, Amy Donaldson, MS, Richard Holubkov, PhD, Teresa Liu, MPH, Stephanie Bisping, BSN, RN, CCRP, Spencer Hawkes, MS, CCRC, Rene Enriquez, BS, Linda Herrera, MPH; Children's Hospital of Pittsburgh, Pittsburgh, PA: Joseph Carcillo, MD, Michael Bell, MD, Alan Abraham, BA; Children's National Medical Center, Washington DC: Murray Pollack, MD, John Berger, MD, Angela Wratney, MD, Jean Reardon, BSN, RN; Children's Hospital of Michigan, Detroit, MI: Kathleen L. Meert, MD, Sabrina Heidemann, MD, Maureen Frey, PhD, RN; Arkansas Children's Hospital, Little Rock, AR: KJS Anand, MBBS, DPhil, Parthak Prodhan, MD, Ronald Sanders, MD, Glenda Hefley, MNsc, RN; Seattle Children's Hospital, Seattle, WA: Jerry Zimmerman, MD, PhD, David Jardine, MD, Ruth Barker, RRT; Children's Hospital Los Angeles, Los Angeles, CA: Christopher J.L. Newth, MB, ChB, J. Francisco Fajardo, CLS (ASCP), RN, MD;

Mattel Children's Hospital at University of California Los Angeles, Los Angeles, CA: Rick Harrison, MD; University of Virginia Children's Hospital, Charlottesville VA: Douglas F. Willson, MD; National Institute of Child Health and Human Development, Bethesda, MD: Carol Nicholson, MD, Tammara Jenkins, MSN RN; From CDC: Karen Broder, MD, Fatima Coronado, MD, MPH, Kristin Brown, MPH, Andrew Baughman, PhD, Ismael Ortega-Sanchez, PhD, Margaret Cortese, MD, MPH, Barbara Slade, MD, Alison Mawle, PhD, Nancy E. Messonnier, MD, and Benjamin Schwartz, MD (now at CARE)

REFERENCES

1. Mattoo S, Cherry JD. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to *Bordetella pertussis* and other *Bordetella* subspecies. *Clin Microbiol Rev.* 2005; 18(2):326–382. [PubMed: 15831828]
2. Cherry JD. Defining Pertussis Epidemiology: Clinical, Microbiologic and Serologic Perspectives. *The Pediatric Infectious Disease Journal.* 2005; 24(5):S25–S34. [PubMed: 15876920]
3. Christie CD, Baltimore RS. Pertussis in neonates. *Am J Dis Child.* 1989; 143(10):1199–1202. [PubMed: 2801662]
4. Halperin SA. Pertussis--a disease and vaccine for all ages. *N Engl J Med.* 2005; 353(15):1615–1617. [PubMed: 16221785]
5. Halperin SA. The control of pertussis--2007 and beyond. *N Engl J Med.* 2007; 356(2):110–113. [PubMed: 17215528]
6. Namachivayam P, Shimizu K, Butt W. Pertussis: severe clinical presentation in pediatric intensive care and its relation to outcome. *Pediatr Crit Care Med.* 2007; 8(3):207–211. [PubMed: 17417115]
7. Surridge J, Segedin ER, Grant CC. Pertussis requiring intensive care. *Arch Dis Child.* 2007; 92(11):970–975. [PubMed: 17611239]
8. Nicholson CE. Critical pertussis may model organ failure in critical illness and injury. *Pediatr Crit Care Med.* 2007; 8(3):288–289. [PubMed: 17496512]
9. Nicholson CE, Coronado F. Critical Pertussis in U.S. Children: Severe Morbidity, Sequelae, and Mortality: A Prospective Cohort Study In. 2008
10. Pertussis--United States, 2001–2003. *MMWR.* 2005; 54(50):1283–1286. [PubMed: 16371944]
11. Beier D, Gross R. The BvgS/BvgA phosphorelay system of pathogenic *Bordetellae*: structure, function and evolution. *Adv Exp Med Biol.* 2008; 631:149–160. [PubMed: 18792687]
12. Konig J, Bock A, Perraud AL, et al. Regulatory factors of *Bordetella pertussis* affecting virulence gene expression. *J Mol Microbiol Biotechnol.* 2002; 4(3):197–203. [PubMed: 11931547]
13. National, state, and urban area vaccination coverage among children aged 19–35 months--United States, 2004. *MMWR.* 2005; 54(29):717–721. [PubMed: 16049420]
14. Jajosky RA, Hall PA, Adams DA, et al. Summary of notifiable diseases--United States, 2004. *MMWR.* 2006; 53(53):1–79. [PubMed: 16775578]
15. Murphy TV, Slade BA, Broder KR, et al. Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR.* 2008; 57(RR-4):1–51. [PubMed: 18509304]
16. He Q, Mertsola J. Factors contributing to pertussis resurgence. *Future Microbiol.* 2008; 3:329–339. [PubMed: 18505398]
17. Halperin SA, Wang EE, Law B, et al. Epidemiological features of pertussis in hospitalized patients in Canada, 1991–1997: report of the Immunization Monitoring Program--Active (IMPACT). *Clin Infect Dis.* 1999; 28(6):1238–1243. [PubMed: 10451159]
18. Tozzi AE, Pastore Celentano L, Ciofi degli Atti ML, et al. Diagnosis and management of pertussis. *CMAJ.* 2005; 172(4):509–515. [PubMed: 15710944]
19. Sawal M, Cohen M, Irazuzta JE, et al. Fulminant pertussis: a multi-center study with new insights into the clinico-pathological mechanisms. *Pediatr Pulmonol.* 2009; 44(10):970–980. [PubMed: 19725100]
20. Vitek CR, Pascual FB, Baughman AL, et al. Increase in deaths from pertussis among young infants in the United States in the 1990s. *Pediatr Infect Dis J.* 2003; 22(7):628–634. [PubMed: 12867839]

21. Mikelova LK, Halperin SA, Scheifele D, et al. Predictors of death in infants hospitalized with pertussis: a case-control study of 16 pertussis deaths in Canada. *J Pediatr*. 2003; 143(5):576–581. [PubMed: 14615725]
22. Garenne M, Lafon M. Sexist diseases. *Perspect Biol Med*. 1998; 41(2):176–189. [PubMed: 9493399]
23. Montani D, O'Callaghan DS, Savale L, et al. Pulmonary veno-occlusive disease: Recent progress and current challenges. *Respir Med*. 2010
24. Paddock CD, Sanden GN, Cherry JD, et al. Pathology and pathogenesis of fatal *Bordetella pertussis* infection in infants. *Clin Infect Dis*. 2008; 47(3):328–338. [PubMed: 18558873]
25. Long, SS. Pertussis (*Bordetella Pertussis* and *Bordetella Parapertussis*). In: Kliegman, R.; Nelson, WE., editors. *Nelson Textbook of Pediatrics*. 18th ed. Philadelphia: Saunders; 2007. p. 1178–1182.
26. Sabella, C. Pertussis (Whooping Cough). In: McInerney, TK., editor. *American Academy of Pediatrics Textbook of Pediatric Care*. Washington, DC: American Academy of Pediatrics; 2009. p. 2419–2425.
27. Han, YY.; Shanley, TP. Multiple Organ Dysfunction Syndrome. In: Nichols, DG., editor. *Rogers' Textbook of Pediatric Intensive Care*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 283–299.
28. Forsyth KD, Campins-Marti M, Caro J, et al. New pertussis vaccination strategies beyond infancy: recommendations by the global pertussis initiative. *Clin Infect Dis*. 2004; 39(12):1802–1809. [PubMed: 15578403]
29. Romano MJ, Weber MD, Weisse ME, et al. Pertussis pneumonia, hypoxemia, hyperleukocytosis, and pulmonary hypertension: improvement in oxygenation after a double volume exchange transfusion. *Pediatrics*. 2004; 114(2):e264–e266. [PubMed: 15286267]
30. Halasa NB, Barr FE, Johnson JE, et al. Fatal pulmonary hypertension associated with pertussis in infants: does extracorporeal membrane oxygenation have a role? *Pediatrics*. 2003; 112(6 Pt 1): 1274–1278. [PubMed: 14654596]
31. McEniery JA, Delbridge RG, Reith DM. Infant pertussis deaths and the management of cardiovascular compromise. *J Paediatr Child Health*. 2004; 40(4):230–232. [PubMed: 15009556]
32. Taylor A, Butt W, Ciardulli M. The functional outcome and quality of life of children after admission to an intensive care unit. *Intensive Care Med*. 2003; 29(5):795–800. [PubMed: 12595983]
33. Hanekamp MN, Mazer P, van der Cammen-van Zijp MH, et al. Follow-up of newborns treated with extracorporeal membrane oxygenation: a nationwide evaluation at 5 years of age. *Crit Care*. 2006; 10(5):R127. [PubMed: 16961935]
34. Khambekar K, Nichani S, Luyt DK, et al. Developmental outcome in newborn infants treated for acute respiratory failure with extracorporeal membrane oxygenation: present experience. *Arch Dis Child Fetal Neonatal Ed*. 2006; 91(1):F21–F25. [PubMed: 16159956]
35. Caro. Economic Burden of Pertussis and the Impact of Immunization. *The Pediatric Infectious Disease Journal*. 2005; 24(5):S48–S54. [PubMed: 15876924]
36. Lee LH, Pichichero ME. Costs of illness due to *Bordetella pertussis* in families. *Arch Fam Med*. 2000; 9(10):989–996. [PubMed: 11115197]
37. Pichichero ME, Treanor J. Economic impact of pertussis. *Arch Pediatr Adolesc Med*. 1997; 151(1):35–40. [PubMed: 9006526]
38. Zhou F, Santoli J, Messonnier ML, et al. Economic evaluation of the 7-vaccine routine childhood immunization schedule in the United States, 2001. *Arch Pediatr Adolesc Med*. 2005; 159(12): 1136–1144. [PubMed: 16330737]
39. Ortega-Sanchez IR, Lee GM, Jacobs RJ, et al. Projected cost-effectiveness of new vaccines for adolescents in the United States. *Pediatrics*. 2008; 121(Suppl 1):S63–S78. [PubMed: 18174323]
40. Byers RK, Rizzo ND. A follow-up study of pertussis in infancy. *N Engl J Med*. 1950; 242(23): 887–891. [PubMed: 15416918]
41. Baggett HC, Duchin JS, Shelton W, et al. Two nosocomial pertussis outbreaks and their associated costs - King County, Washington, 2004. *Infect Control Hosp Epidemiol*. 2007; 28(5):537–543. [PubMed: 17464912]

42. Calugar A, Ortega-Sanchez IR, Tiwari T, et al. Nosocomial pertussis: costs of an outbreak and benefits of vaccinating health care workers. *Clin Infect Dis*. 2006; 42(7):981–988. [PubMed: 16511764]
43. Centers for Disease Control and Prevention. Guidelines for the Control of Pertussis Outbreaks 2000 (amendments made in 2005 and 2006). 2000. cited Available from: <http://www.cdc.gov/vaccines/pubs/pertussis-guide/guide.htm>
44. Pickering, LK.; Baker, CJ.; Kimberlin, DW.; Long, SS. American Academy of Pediatrics. Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove, IL: American Academy of Pediatrics; 2009. Pertussis (Whooping Cough); p. 504-519.
45. Siegel JD, Rhinehart E, Jackson M, et al. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Health Care Settings. *Am J Infect Control*. 2007; 35(10 Suppl 2):S65–S164. [PubMed: 18068815]
46. Tablan OC, Anderson LJ, Besser R, et al. Guidelines for preventing health-care--associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR*. 2004; 53(RR-3):13–15.
47. Pickering, LK.; Baker, CJ.; Kimberlin, DW.; Long, SS. American Academy of Pediatrics. Red Book: 2009 Report of the Committee on Infectious Diseases. 27th edition. Elk Grove Village, IL: American Academy of Pediatrics; 2009. Infection Control for Hospitalized Children; p. 148-161.
48. Bryant KA, Humbaugh K, Brothers K, et al. Measures to control an outbreak of pertussis in a neonatal intermediate care nursery after exposure to a healthcare worker. *Infect Control Hosp Epidemiol*. 2006; 27(6):541–545. [PubMed: 16755471]
49. Edwards KM, Talbot TR. The challenges of pertussis outbreaks in healthcare facilities: is there a light at the end of the tunnel? *Infect Control Hosp Epidemiol*. 2006; 27(6):537–540. [PubMed: 16755470]
50. Kretsinger K, Broder KR, Cortese MM, et al. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR*. 2006; 55(RR-17): 1–37.
51. Tiwari T, Murphy TV, Moran J. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis, 2005 CDC Guidelines. *MMWR*. 2005; 54(RR-14):1–16. [PubMed: 16340941]
52. De Greeff SC, Dekkers AL, Teunis P, et al. Seasonal patterns in time series of pertussis. *Epidemiol Infect*. 2009; 137(10):1388–1395. [PubMed: 19327200]
53. Bisgard KM, Pascual FB, Ehresmann KR, et al. Infant pertussis: who was the source? *Pediatr Infect Dis J*. 2004; 23(11):985–989. [PubMed: 15545851]
54. Wendelboe. Duration of Immunity Against Pertussis After Natural Infection or Vaccination. *The Pediatric infectious disease journal*. 2005; 24(5):S58–S61. [PubMed: 15876927]
55. Wendelboe AM, Njamkepo E, Bourillon A, et al. Transmission of *Bordetella pertussis* to young infants. *Pediatr Infect Dis J*. 2007; 26(4):293–299. [PubMed: 17414390]
56. Willson DF, Dean JM, Newth C, et al. Collaborative Pediatric Critical Care Research Network (CPCCRN). *Pediatr Crit Care Med*. 2006; 7(4):301–307. [PubMed: 16738501]
57. Greenberg. Summary: Health and Economic Burden of Pertussis. *The Pediatric Infectious Disease Journal*. 2005; 24(5):S55–S57. [PubMed: 15876926]
58. Bouchez V, Caro V, Levillain E, et al. Genomic content of *Bordetella pertussis* clinical isolates circulating in areas of intensive children vaccination. *PLoS One*. 2008; 3(6):e2437. [PubMed: 18560590]
59. Kallonen T, He Q. *Bordetella pertussis* strain variation and evolution postvaccination. *Expert Rev Vaccines*. 2009; 8(7):863–875. [PubMed: 19538113]

Figure 1.

Number of reported pertussis cases, by year – United States, 1922–2006

Source: For 1950–2006, CDC, National Notifiable Diseases Surveillance System; for 1922–1949, passive reports to the U.S. Public Health Service.(15)

Table 1

Reported pertussis-related deaths by age-groups, United States, 1990–2008

Age Group	1990 – 1999	2000 – 2008	<i>p</i> -value
0 – 1 month	68	111	0.30
2 – 3 months	16	56	<0.05
4 – 5 months	5	6	0.52
6 – 11 months	4	1	0.06
1 – 10 years	8	4	<0.05
11 – 17 years	0	2	0.53
18 years	2	6	0.71
Total (all ages)	103	186	

Source: Centers for Disease Control

Table 2

CPCCRN Patient Population 2008

Hospital	Ethnicity or Race (%)					Total Admissions
	NHW	H	AA	NA	A/PI	
Arkansas Children's Hospital	66.9	5.0	24.8	0.1	0.7	2,122
Children's Hospital of Los Angeles	16.9	57.6	6.7	0.1	7.5	1,740
Children's Hospital of Michigan	39.5	2.7	42.3	0.1	0.6	1,420
Children's National Medical Center	32.1	15.0	41.9	0.0	2.3	2,216
Seattle Children's Hospital	51.9	15.0	5.7	1.7	6.4	1,862
Mattel Children's Hospital UCLA	43.0	44.5	5.4	0.5	4.3	933
Children's Hospital of Pittsburgh	79.3	3.0	13.8	0.0	0.6	2,085
Total Admissions (2008)	48.5	18.1	21.1	0.3	3.0	12,378

NHW = non-Hispanic White; H = Hispanic; AA = African-American; NA = Native American; A/PI = Asian or Pacific Islander