Can We Conquer Coqueluche?

Ruth Lynfield1 and William Schaffner2

1Minnesota Department of Health, St. Paul; and 2Department of Preventive Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

Keywords. pertussis; Bordetella pertussis; pertussis vaccine; pertussis epidemiology.

“The child at first has the symptoms of an ordinary cold in the head and thorax, accompanied by sharp nervous coughs which have a tendency to come in series. This gradually increases until there is a succession of violent coughs accompanied by a feeling of suffocation and flushing of the face. It is frequently stated that the child ‘coughs until it is black in the face. . . . As soon as the cough has ceased, the little sufferer endeavors to fill up its lungs again, but there is a nervous spasm of the muscles of the throat which narrows the opening through which the air must pass. The violent attempt to inspire the air through this small space produces the familiar ‘whoop’ from which the disease receives its name.”

This clinical description of pertussis, or as it is known in French, coqueluche, was written by W. C. Rucker, assistant surgeon general of the US Public Health Service, in 1912 [1]. It remains, 101 years later, an apt description of classic pertussis. Notably, the term “pertussis” is derived from Latin, meaning “intense cough.”

Bordetella pertussis, the bacterium that causes pertussis, is spread easily via aerosolized droplets from coughing or sneezing. Pertussis is thought to have a secondary attack rate of 80% among susceptible household contacts [2]. Among susceptible individuals, the disease usually starts with mild symptoms that may include a runny nose, low grade fever, and occasional cough (the catarrhal stage). After 1–2 weeks, severe coughing begins that may include a forced inhale or “whoop” (the paroxysmal stage). This stage can last 1–6 weeks and is followed by a convalescent stage, lasting 2–3 weeks, in which the number of coughing fits decreases. Because of the length of clinical symptoms, pertussis has been called the “hundred day cough.”

Pertussis can be life threatening, especially for infants. More than half of infected infants require hospitalization for complications, including apnea (67%), pneumonia (23%), and, less frequently, seizures (1.6%) and encephalopathy (0.4%). One to two percent of hospitalized infants, die [3]. Marked lymphocytosis and pulmonary edema may develop, particularly in critically ill infants. Infection is generally milder in older children and adults. Immunized individuals with pertussis usually have less severe disease and may not have the classic symptoms. Nevertheless, the illness is not trivial; coughing paroxysms may be so arduous and sustained that they can result in fractures of ribs and vertebrae, urinary incontinence, and syncope. Early treatment with antibiotics (before coughing paroxysms) can make the disease less severe and less likely to spread to close contacts. Persons infected with B. pertussis can transmit the bacterium from the beginning of the catarrhal stage through the third week after the onset of paroxysms or until 5 days after the start of effective antibiotic therapy. The incubation period is generally 7–10 days, with a range of 4–21 days.

Whooping cough was a major cause of childhood deaths in the first part of the twentieth century, with thousands of children dying each year. Children <1 year of age had the highest mortality rate; it was >200 cases/100 000 until the 1930s. In 1910, there was an average of 1 death per 10 cases [4]. B. pertussis is a gram-negative cocccobacillus and was first visualized in sputum from an infected Belgian girl, the daughter of Jules Bordet, in 1900. Bordet and Octave Gengou succeeded in isolating the organism from the sputum of Bordet’s son 6 years later, when the
The vaccine became widely available in the United States in 1940 and was approved by the American Academy of Pediatrics in 1943 [8]. A combination vaccine that included diphtheria and tetanus toxoids in addition to inactivated *B. pertussis* was licensed in 1948. The reported incidence of pertussis dropped from 150–250 cases/100 000 persons (>200 000 cases) before widespread use of vaccine to a low of 0.5 cases/100 000 in 1976, when only 1010 cases were reported nationally [9]. Because of concerns regarding side effects, such as fever, persistent crying, febrile seizures, and, rarely, hypotonic-hyporesponsive episodes related to the whole-cell vaccine [10], acellular, or subunit, pertussis vaccines were developed. In the United States, acellular vaccine formulations replaced whole-cell booster vaccines in 1992 and primary series vaccines in 1997.

During the 1980s, coverage with ≥3 doses of pertussis vaccine exceeded 95% among US children, as measured at school entry [11]. However, despite this near-universal use of pertussis vaccines in childhood, the incidence of pertussis in the United States began to rise. Notably, infections were occurring in adolescents and adults. In 2004, almost 26 000 cases of pertussis were reported to the Centers for Disease Control and Prevention (CDC); adults accounted for 29% of cases and adolescents for 34% of cases [9]. Vaccine-associated immunity was thought to wane after 5–10 years; in addition, immunity after infection, in contrast to that for certain other infectious diseases, was known not to be lifelong. Notably, unrecognized infections in older age groups were often the source of infections in infants. In 2006, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) was recommended for adolescents, adults, and postpartum women [9, 12]. To further decrease infections in infants, recommendations for Tdap were updated in 2011 to include pregnant women and emphasized vaccination for persons who have close contact with infants [13]. In 2012, recommendations were issued to vaccinated women with each pregnancy [14].

During the past 3 years, large outbreaks of pertussis have occurred in the United States. In 2010 in California, there were >9000 cases, 809 hospitalizations, and 10 deaths due to pertussis. All deaths and most hospitalizations occurred in infants younger than 3 months of age. High rates of disease were observed in fully vaccinated children, especially those aged ≤10 years [15]. In Wisconsin in 2012, >6400 cases were reported, with an incidence of approximately 113 cases/100 000 persons. The median age was 12.3 years, and among cases aged ≤10 years, 73% were appropriately vaccinated. Notably, 79% of case patients 11–18 years of age had received Tdap before cough onset [16]. In Washington, from January to 16 June 2012, there were 2520 cases (37.5 cases/100 000), and 75% of case patients aged 3 months to 10 years were appropriately vaccinated [17]. Overall, preliminary CDC data for 2012 comprised approximately 42 000 cases, the highest number in 57 years [18]. As reflected in Wisconsin and Washington, half of the cases nationally occurred in the 7–19-year-old age group, an age group that has been well vaccinated [19]. The number of reported cases is likely a fraction of the true number of cases, because many case patients do not seek medical care, and of those who do, a specific case definition must be met. Pertussis consumes significant healthcare resources in terms of direct healthcare costs, for the evaluation and treatment of an infected individual, and public health costs, for minimizing spread. The cost for investigating an outbreak of pertussis has been estimated at >$2000/case, a substantial sum for resource-strapped public health agencies [20]. The reasons for the resurgence of pertussis in the United States are not clear. Contributions may include waning immunity, particularly that associated with acellular pertussis vaccines; heightened and improved diagnosis; and genetic changes in the organism.

Pertussis remains a major cause of morbidity and mortality globally. According to the World Health Organization, an estimated 50 million pertussis cases and 300 000 deaths occur each year. Case-fatality rates in countries with limited resources are up to 4% among infants [21]. Pertussis has also made a comeback in resource-secure countries that have good immunization and surveillance programs. Despite use of different vaccine types (including acellular and/or whole-cell vaccines), vaccine schedules, and surveillance methods, outbreaks and increases in case numbers have been reported in Australia, Canada, Europe, and Latin America.

On 6 March 2013, the Infectious Diseases Society of America, the National Foundation for Infectious Diseases, the Pediatric Infectious Diseases Society, and the National Vaccine Program Office (NVPO) convened a meeting with scientists from the CDC, the National Institutes of Health, the Food and Drug Administration, the NVPO, academia, industry, and public health agencies to discuss the resurgence of pertussis and develop priorities for research and response. The agenda included review and discussions of epidemiology, pathogenesis, human immune response to disease and vaccine, mouse and pig models of pertussis, nonhuman primate models, current status of vaccine development, and regulatory issues. The group discussed potential interim and long-term solutions. This supplement of the *Journal of Infectious Diseases* is intended to share the information presented and discussed at the meeting. It is our hope that it will inspire scientists and public health practitioners to use state of the art science and knowledge to develop a twenty-first century approach to the prevention and control of pertussis. Indeed, lessons learned from this work will surely have applications in the control of other infectious diseases.
As you read this issue and consider new approaches, please keep in mind the words of Dr William Colby Rucker, who wrote >100 years ago, “Whooping cough is a danger to be avoided and combated in the interest of humanity and the citizens of tomorrow” [1]. We hope that in the future we will be able to fully achieve this objective.

Notes

Financial support. This work was supported in part by the Centers for Disease Control and Prevention’s Emerging Infections Program (cooperative agreement).

Potential conflicts of interest. W. S. has receiving funding from Sanofi-Pasteur, Dynavax, and Pfizer and is a member of the data safety monitoring board for Merck. R. L. certifies no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

13. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine in pregnant women and persons who have or anticipate having close contact with an infant aged less than 12 months—Advisory Committee on Immunization Practices, 2011. MMWR Morb Mortal Wkly Rep 2011; 60:142–46.