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Whooping Cough in 2014 and Beyond
An Update and Review

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Pertussis, or whooping cough, has had a dramatic resurgence in the past several years and is the most common vaccine-preventable disease in the world. The year 2012 marked the most cases in the United States in >50 years. Large outbreaks have occurred in multiple states, and infant deaths have drawn the attention of not only health-care providers but also the media. Although the disease is theoretically preventable by vaccination, it remains a challenge to control. New vaccination strategies have been implemented across different age groups and populations of patients, but vaccine coverage remains dismally low. Acellular vaccines, although safe, do not afford the same long-lasting immunity as the previously used whole-cell vaccine. Ultimately, improvements in the development of vaccines and in vaccination coverage will be essential to decrease the burden of pertussis on society. This article provides a review of pertussis infection and discusses advances related to the epidemiology, diagnosis, treatment, and prevention of infection, as well as continued areas of uncertainty.

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ABBREVIATIONS: CDC = Centers for Disease Control and Prevention; DTaP = diphtheria-tetanus toxoids, acellular pertussis; PCR = polymerase chain reaction; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis

Pertussis, or whooping cough, is an ancient disease that continues to cause significant morbidity and mortality.[1] There has been a dramatic resurgence of pertussis in the past several years. This was most evident in 2012, when the highest number of cases in 50 years was reported in the United States.[2] Large outbreaks have occurred in multiple states, and infant deaths have drawn the attention of not only health-care providers but also the media. Despite the advent of polymerase chain reaction (PCR) tests, the disease remains underdiagnosed, likely because of a lack of recognition and consideration for testing. Treatments are mainly aimed at preventing spread and have little impact on the course of the disease. New vaccination strategies have been implemented across different age groups and patient populations, to include pregnant women and the elderly, but vaccine coverage remains dismally low.[3-6] Acellular vaccines, although safe, may not afford the same long-lasting immunity as the previously used whole-cell vaccine. Unless we can improve vaccine efficacy and coverage,

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pertussis will continue to be a significant health threat worldwide. This article reviews advances in the epidemiology, diagnosis, treatment, and prevention of pertussis infection and highlights areas of uncertainty (Table 1).

Definition

Multiple case definitions for pertussis exist worldwide, making it difficult to define the disease from a clinical perspective and to determine the true epidemiologic burden of disease.[7] Most definitions are categorized as confirmed or probable and vary depending on the context in which they are used (ie, vaccine trials, outbreaks, and so forth). The US Centers for Disease Control and Prevention (CDC) definition is provided in Table 2 and can serve as the working case definition at this time.[8] Similar to the CDC definition, most definitions worldwide are a decade old and based largely on the clinical presentation in infants and children. With an increasing burden of disease in adolescents and adults, new definitions have been proposed in an attempt to improve the sensitivity and specificity of diagnosis. The increased use of PCR testing and its inclusion in updated definitions is being evaluated, with hope of providing more accurate definitions of clinical disease. Studies are needed to validate these definitions and determine their usefulness. A thorough review of the topic, including the proposed definitions and their scientific basis, was recently published.[7]

Microbiology

Pertussis is primarily caused by the gram-negative coccobacillus, *Bordetella pertussis.* However, other species of *Bordetella*, most notably *Bordetella parapertussis* and *Bordetella bronchiseptica*, can cause mild or moderate pertussis-like symptoms.[9-11] Of interest to pet owners, *B bronchiseptica* is the cause of kennel cough. More recently, cases of *Bordetella holmesii* have been identified during pertussis outbreaks that have particularly affected adolescents. In a community outbreak in Ohio, 60% of *B holmesii* case patients had received tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine, thus questioning the effectiveness of the vaccine in prevention of illness secondary to this particular species.[11,12] The emergence of *B holmesii* has been observed in other countries as well.[13-15]

Variation in the expression of pertussis virulence factors has been reported in recent years, prompting questions regarding the efficacy of the Tdap vaccine in the presence of these novel strains. Pertactin, a highly immunogenic virulence factor of *B pertussis*, is currently one of the main components of the acellular vaccine. To our knowledge, pertactin-negative strains were first reported in France,[16] and researchers in Philadelphia described pertactin-negative strains in 11 isolates for the first time in the United States in 2013.[17] Other countries had previously reported similar results, thus highlighting the need for ongoing research into the different variants of pertussis, in particular those isolated from previously vaccinated patients who develop disease.[18] The long-term consequences of these changes are unknown, but a recent study from France reported no clinical difference in infants (aged $<$ 6 months) when comparing pertactin-positive and pertactin-negative isolates.[19]

Pertussis is an acute airway infection that is localized to the airway and does not commonly enter the circulation and disseminate. Although pertussis harbors a multitude of toxins, including pertussis toxin, adenylate cyclase toxin, and tracheal toxin, the mechanism of the paroxysmal cough is not known. The most accepted explanation is that respiratory cilia are damaged by both the toxins and the resultant host immune response, resulting in irritation and subsequent coughing spells.[20] There is no long-term human carriage or animal reservoir, and *B pertussis* does not survive for long periods in the environment. These characteristics should in theory

TABLE 1] Key Updates for Pertussis

Update
There were more pertussis cases in 2012 compared with any other year in the past 50 years.
Consider testing for pertussis in any patient with cough lasting $>$2 wk who meets the pertussis clinical case definition.
Pertussis testing with culture, polymerase chain reaction, and serology should be performed based on the clinical stage of disease.
Treatment of pertussis remains limited, as antibiotics are mainly used to prevent spread.
In the United States and worldwide, pertussis vaccination rates are dismally low.
Pertussis vaccination is recommended for all adults, and methods for increasing vaccination coverage should be explored.
Pregnant women need to be vaccinated against pertussis with each pregnancy.