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Pertussis: Microbiology, Disease, Treatment, and Prevention

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SUMMARY

Pertussis is a severe respiratory infection caused by *Bordetella pertussis*, and in 2008, pertussis was associated with an estimated 16 million cases and 195,000 deaths globally. Sizeable outbreaks of pertussis have been reported over the past 5 years, and disease reemergence has been the focus of international attention to develop a deeper understanding of pathogen virulence and genetic evolution of *B. pertussis* strains. During the past 20 years, the scientific community has recognized pertussis among adults as well as infants and children. Increased recognition that older children and adolescents are at risk for disease and may transmit *B. pertussis* to younger siblings has underscored the need to better understand the role of innate, humoral, and cell-mediated immunity, including the role of waning immunity. Although recognition of adult pertussis has increased in tandem with a better understanding of *B. pertussis* pathogenesis, pertussis in neonates and adults can manifest with atypical clinical presentations. Such disease patterns make pertussis recognition difficult and lead to delays in treatment. Ongoing research using newer tools for molecular analysis holds promise for improved understanding of pertussis epidemiology, bacterial pathogenesis, bioinformatics, and immunology. Together, these advances provide a foundation for the development of new-generation diagnostics, therapeutics, and vaccines.

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INTRODUCTION

Aim of This Review

Despite the recognition of pertussis clinical disease more than 1,600 years ago, *Bordetella pertussis* continues to be a major global pathogen now known to affect infants, children, and adults. Despite major disease reductions due to the introduction of pertussis vaccines in the 1940s and vaccine improvements in the 1970s, epidemics of pertussis persist. The aim of this review is to provide state-of-the art information on pertussis, including history of the disease and causative organism, pathogenesis, epidemiology and burden of the disease, clinical presentation and complications, prevention and treatment modalities, outbreak control, immunity as a result of vaccination and disease exposure, and future directions.

History of Pertussis and *Bordetella pertussis*

In the seventh century, during the Sui Dynasty, a pertussis-like illness was described by Chinese medical scholar Yuanfang Chao as "the cough of 100 days" (1, 2). One thousand years later (1578) in France, Guillaume De Baillou provided the first description of whooping cough among children of Paris; he described the illness as "quinte" due to the observed 5-h periodicity of paroxysms seen in acute episodes of disease (3). Recent research suggests that the earliest recorded epidemics of pertussis were noted in Persia (present-day Iran) (4). In Europe, pertussis outbreaks were first described in the 16th century, but recognition of the causative agent did not occur until 300 years later. In 1883, a German scientist, Carl Burger, working at the University of Bonn recognized rods of bacteria in a stained sputum specimen from a patient with clinical pertussis (5). Seventeen years later, Jules Bordet, a Belgian physician-scientist, visualized small Gram-negative bacilli in the sputum of his 5-month-old daughter suffering from whooping cough. However, at the time, Bordet was unable to grow these bacilli in available culture media (6, 7). Six years later, Bordet's son had also suffered from pertussis, and by that time, Bordet and Gengou were successful in isolating and growing *B. pertussis* for the first time in history (6, 8–10). In 1920, Bordet was awarded the 1919 Nobel Prize in Physiology or Medicine for his work related to antimicrobial immunology, which included extensive study of *B. pertussis* and set the stage for identification of this organism as the cause of whooping cough (11).

Microbiology of *Bordetella* Species

Bordetella species are classified under the family *Alcaligenaceae* and comprise 10 genetically distinct species (Table 1) (12–14). Although *B. pertussis* has been classically identified as the sole agent responsible for whooping cough, other species (i.e., *B. parapertussis* and *B. holmesii*) can also cause coughing that resembles whooping cough (15–28). *B. pertussis* is a Gram-negative, pleomorphic aerobic coccobacillus that grows optimally on either Bordet-Gengou or Regan-Lowe agar between 35°C and 37°C and can be differentiated from other *Bordetella* species based on its growth and biochemical characteristics. *B. pertussis* is a fastidious, nonmotile, catalase- and oxidase-positive species, in contrast with *B. parapertussis*, which is less fastidious, oxidase negative, and urease positive and produces a brown pigment on heart infusion, Regan-Lowe, or Mueller-Hinton agar (12, 13, 29–32). *Bordetella* species grow slowly on blood-supplemented medium and on synthetic medium containing appropriate growth factors, such as nicotinamide (30).

TABLE 1 *Bordetella* species and their associated hosts

Bordetella species (references)	Associated host organism(s)
B. pertussis (58, 594)	Only human
B. parapertussis (26, 27, 47, 595–598)	Human, sheep, goat, pig
Bovine-associated *B. parapertussis* (14, 599)	Cattle
B. bronchiseptica (49–54, 600)	Human, pig, cat, dog, rabbit
B. avium (601–604)	Human, bird
B. hinzii (17, 605–611)	Human, bird
B. holmesii (16, 28, 36, 353, 504, 611–614)	Human
B. trematum (21, 611, 615, 616)	Human
B. petrii (617, 618)	Human
"*B. ansorpii*" (619, 620)	Human

Other *Bordetella* species have been shown to infect humans as well as animals. Although *B. parapertussis* and *B. holmesii* have been recognized as causes of whooping cough-like illness, *B. parapertussis* has been studied more widely than *B. holmesii* (15, 16, 28, 33–36). Cherry and Seaton analyzed nasopharyngeal specimens submitted for PCR testing from nine states (California, Florida, Illinois, Michigan, New Jersey, Ohio, Texas, Virginia, and Washington) between 2008 and 2010 (27). The results of this study revealed that ~14% of the culture-positive clinical specimens were identified as *B. parapertussis*. However, additional studies between 1971 and 2003 have shown wide variation in detection rates for *B. parapertussis*; rates ranged from 1.4% to 97.7% (24–26, 37–43). These studies differed in geographic location, PCR methods, and the number of clinical samples tested.

In humans, *B. parapertussis* and *B. holmesii* can cause disease, although the severity of symptoms tends to be milder than seen with *B. pertussis* (26, 27, 34, 44–46). *B. parapertussis* may cause disease in domestic animals, including ovine (sheep) and swine (14, 47), though the strains infecting these mammalian species arise from different lineages and are genetically distinct (48). In addition, *B. bronchiseptica* has been identified as a cause of disease among immunocompromised persons and has been isolated from traumatized patients and patients with peritonitis (49–52) and from domestic dogs, cats, and pigs (52–54).

PATHOGENESIS AND HISTOPATHOLOGICAL FINDINGS OF PERTUSSIS

Mechanisms of Pathogenesis

Although *B. bronchiseptica*, *B. parapertussis*, and *B. holmesii* can infect a wide range of mammals, including humans, *B. pertussis* is a human-specific pathogen (55–58). Pertussis results from a coordinated interplay of several virulence factors of *B. pertussis*, which include toxins such as pertussis toxin (PT), adenylate cyclase toxin (AC), dermonecrotic toxin (DNT), and tracheal cytotoxin (TCT). Other factors that influence the virulence of *B. pertussis* include surface structures, such as filamentous hemagglutinin (FHA), fimbriae (FIM), pertactin (PRN), the type III secretion system, and lipopolysaccharide (LPS) (59), and metabolic proteins (e.g., BrkA, BapC, and BatB) (Table 2) (60–132). In *B. pertussis*, the *bvgAS* genes positively control expression of several virulence factors, including PT, AC, DNT, FHA, TcfA, pertactin, FIM, BrkA, BipA, BcfA, and Vag8. The BvgAS two-component signal transduction system of *B. pertussis* plays a pivotal role in pertussis pathogenicity (133, 134).

TABLE 2 Virulence factors of *Bordetella pertussis*[a]

Virulence factor (reference[s])	Structure	Location	Action, function, and role in immunity
PT (63, 64, 621–627)	Composed of 5 subunits (94 kDa): ADP-ribosylating AB_5-type exotoxin, A (S1) catalytic subunit and B (S2 to S5) subunits	Periplasm	Production of functional PT is unique to *B. pertussis*; S1 subunit, ADP-ribosyltransferase (G protein ribosylation); S2 to S5 subunits, bind target cell receptors; sensitizes to histamine, induces lymphocytosis and insulin secretion, and modifies T-cell responsiveness; component of acellular vaccines
AC (67–69, 71, 72, 74, 77–79, 628–633)	Two functional C- and N-terminal domains (25 and 18 kDa, respectively); activated by calmodulin and generates cAMP	Extracytoplasmic	Binds target cells via C-terminal domain; converts ATP to cAMP via N-terminal domain; enzymatically active hemolysin; inhibits migration and activation of phagocytes; blocks induction of bactericidal nitric oxide in macrophages; suppresses cytotoxic effect of neutrophils, monocytes, and natural killer cells; suppresses activation and chemotaxis of T cells; natural infection and DTP vaccination induce antibodies to AC
DNT (100, 102, 104, 634)	Heat-labile toxin; typical A-B bacterial toxin (160 kDa)	Cytoplasm	Positively regulated by BvgAS system; no clear role in pathogenesis; vasoconstriction in primates; induces cell necrosis *in vitro*; *B. bronchiseptica* DNT impairs osteoplastic cell differentiation in pigs
T3SS (80, 81, 86–88, 91, 92, 163, 635)	Needle-like structure; proteins secreted by T3SS include Beta A, BopN, BopD, and Bsp22	Cell envelope	Translocates effector proteins into host cells, induces cell necrosis *in vitro*, subverts innate and adaptive immune responses during infection of lungs; Beta A. cytotoxicity *in vitro* (mechanism not well understood); BopN, turns off host inflammatory reaction
TCT (94, 95, 97, 98, 143, 636, 637)	Disaccharide-tetrapeptide monomer of peptidoglycan (9.2 kDa)	Extracellular space	Produced during cell wall remodeling, acts synergistically with lipopolysaccharide toxin to stimulate production of pro-inflammatory cytokines (TNF-α, IL-1α, IL-1β, and IL-6), induces nitric oxide synthase for nitric oxide production, and damages ciliated cells; hypothesized to cause the "whoops" and/or cough paroxysms
FHA (106–108, 110, 112, 145, 638–644)	Hairpin-shaped, surface-associated, and secreted protein (220 kDa); heparin binding domain, Arg-Gly-Asp, and Chinese hamster ovary recognition domain; FHA and filamentous hemagglutinin transporter protein (FhaC) function as prototypical members of secretion pathway	Cell wall	Mediates initial adhesion of *B. pertussis* to ciliated epithelium of upper respiratory tract; essential for progression of infection from upper to lower respiratory tract; promotes phagocytosis of *B. pertussis* by macrophages and polymorphonuclear neutrophils; induces release of IL-6 and IL-10; suppresses IL-12 production by macrophages and dendritic cells
FIM (type I pili) (113–117, 645–647)	Type 2 and 3 *fim* products represent serotype-specific AGG; *fim* strains are susceptible to change and polymorphism; FimD antigen is common to all fimbriae	Surface projections	Fim 2 and 3 are important components for colonizing lower respiratory mucosa, involved in adherence and suppression of the initial inflammatory response to infection; AGG present in all whole-cell vaccines; FIM antigens may be present in minute quantities in acellular vaccines
PRN (118–120, 141, 647–651)	Autotransporter protein mediates eukaryotic cell binding via Arg-Gly-Asp motif, highly immunogenic, highly polymorphic (prn1 to prn11) (69 kDa)	Surface	Resists neutrophil-mediated clearance; contributes to adherence of *B. pertussis* to ciliated respiratory epithelium in rabbits; changes in *prn* types resulted in less efficacious whole-cell vaccine; PRN2 and PRN3 are the most common circulating *prn* strain types; PRN1 antigen is present in many acellular vaccines; PRN antigenic variation in vaccines is implicated in escape from immunity to *B. pertussis*
TcfA (652)	Autotransporter protein (60 kDa)	Surface, secreted	Tracheal colonization
Lipopolysaccharide (59, 121–123, 125, 653)	Endotoxin	Surface	Induces fever after administration of whole-cell vaccine; antigenic and adjuvant properties but not protective; not a component of acellular vaccines
BrkA, BapC, BatB, Vag8, SphB1, Phg (129, 130, 163, 652, 654–658)	BvgAS-activated classical autotransporter proteins; BrkA (73 kDa) for N-terminal domain and 30 kDa for outer membrane C-terminal protein; Vag8 (95 kDa)	Surface	Mediates adherence, resists complement, evasion of antibody-mediated clearance, and proteolytic processing of other surface proteins; SphB1 is required for FHA maturation; BrkA is a bactericidal resistance factor

[a] PT, pertussis toxin; AC, adenylate cyclase toxin; cAMP, cyclic AMP; DNT, dermonecrotic toxin; T3SS, type III secretion system; TCT, tracheal cytotoxin; FHA, filamentous hemagglutinin; FIM, fimbriae; AGG, agglutinogens; PRN, pertactin; TcfA, tracheal colonization factor.

Like that of other bacteria, *B. pertussis* pathogenesis is influenced by environmental cues (e.g., temperature changes) that dictate virulence factor expression once inside the human host. During transmission from person to person, *B. pertussis* moves from local environmental temperatures to higher body temperatures which appear to influence regulation of the *bvgA* and *bvgS* genes (135). In turn, the regulatory system encoded by *bvgA* and *bvgS* can be activated by temperature (as well as sulfate

[SO_4] and nicotinate) and regulates expression of virulence factors in *B. pertussis* and *Escherichia coli* (136–138). Recent insights by Boulanger et al. suggest that *bvgA* regulates *fim3* gene expression through phosphorylation-mediated control of transcriptional complexes (139). In addition, comparative genomics work by Bart and colleagues examining single nucleotide polymorphisms (SNPs) underscores the importance of genetic changes in *B. pertussis* that play a role in altered transcription and translation (140).

Clinical observations combined with studies in animal models suggest that the mechanisms of virulence of *B. pertussis* consist of a cascade of events initiated by the adherence of bacteria via FHA and fimbriae to tracheal epithelium and lungs as an essential primary step (141, 142). Once adherence takes place, *B. pertussis* cells multiply locally, resist host defense mechanisms (e.g., mucociliary clearance, antimicrobial peptides, and inflammatory cells), and cause local damage to the upper and lower respiratory tracts with systemic manifestations (143–145). The severity of the symptoms depends on several factors, including the patient's age, strength of the immune response, and extent of systemic bacterial dissemination. In infants, for whom disease is severe, bacteria descend from the upper to the lower respiratory tract and, via an unclear mechanism, produce necrotizing bronchitis, diffuse alveolar damage, intra-alveolar hemorrhage, fibrinous edema, macrophage-rich alveolar infiltrates, lymphangiectasia, neutrophilic bronchopneumonia, and fibrin thrombi (142, 143, 146). In more severe cases, these pathological events can lead to pulmonary hypertension, respiratory failure, and even death (142, 147, 148). Pulmonary hypertension develops as an indirect effect of PT through induction of lymphocytosis (hyperleukocytosis), in which the total white blood cell (WBC) count can exceed 1×10^5 cells/mm^3. These extremely high WBC counts produce lymphocyte aggregations in the pulmonary vasculature that result in increased pulmonary vascular resistance (149–151). In infants with pertussis, the lymphoid system is also affected. Postmortem biopsies have shown cortical atrophy of the thymus gland, lymph depletion in lymph nodes, and white pulp depletion in spleen (152). In infants who had encephalopathy secondary to *B. pertussis* infection, brain biopsies showed cerebral hemorrhage and cortical atrophy (153, 154). Although these pathological findings could result from the direct effect of *B. pertussis* toxins on the brain, they are thought to result from hypoxia (145).

Despite recent advances in *B. pertussis* research in the past 2 decades, much remains unknown about the pathogenesis of pertussis (143, 146). For instance, the precise mechanism underlying the paroxysmal cough-associated pertussis "whoops" has not been clearly identified, though some researchers suggest that TCT may be responsible (143). In addition, although several *B. pertussis* virulence factors have been studied, the interaction and synergistic activity of these factors (e.g., PT, LPS, and TCT), which determines the clinical progression and spectrum of disease across different age groups, require additional study (146). Further studies on the pathogenesis of *B. pertussis* may also provide the basis for design of novel antimicrobial agents that interfere with newly identified virulence mechanisms.

EPIDEMIOLOGY

Global Burden of Pertussis

Pertussis is an endemic disease in developing and developed countries, with frequent outbreaks occurring sporadically at different places around the world. In 1999, Crowcroft et al. estimated the global incidence of pertussis to be 48.5 million cases, with approximately 295,000 deaths reported (155). In 2010, Black et al. reported that 16 million cases of pertussis occurred in 2008 worldwide, resulting in 195,000 deaths (156). A large number of deaths (83,580) were reported from Africa (156, 157). In 2013, an estimated 136,000 cases worldwide were reported (158, 159).

There are several challenges in estimating the global pertussis disease burden. First, many countries have limited surveillance infrastructure, which does not facilitate timely reporting of clinically suspected pertussis cases. Second, in developing countries, laboratory infrastructure to support routine pertussis testing is limited, and molecular diagnostic tests such as PCR are not uniformly available (160). Third, in areas with few trained health professionals, inconsistent clinical identification of pertussis disease may hinder case reporting. In addition, the WHO has noted that the application of a standardized set of pertussis case definitions within an overall surveillance framework for vaccine-preventable diseases or communicable diseases has not been uniform (161, 162).

In 2014, the Strategic Advisory Group of Experts (SAGE) on immunizations charged a pertussis working group to review the current global landscape of pertussis (161). The SAGE review described the epidemiology of pertussis, the effectiveness and safety of various immunization strategies and schedules, and pertussis-related outcomes for 21 countries. For this review, data were collected using a standardized questionnaire consisting of several outcomes and data elements, including incidence of pertussis, clinical case definition, surveillance methods used, pertussis vaccine given, rates of vaccine coverage, and vaccination schedules. The working group found that the evaluation of pertussis incidence is a complex task at the global and country levels. Estimating the burden of pertussis has been a major challenge due to several factors, including changes in surveillance and diagnostic methods over time, changes in national vaccine schedules for and compositions of diphtheria toxoid–tetanus toxoid–whole-cell pertussis (DTP) or diphtheria toxoid-tetanus toxoid-acellular pertussis (DTaP) vaccines, and changes in vaccine manufacturers (161).

A key challenge in estimating the burden of pertussis relates to differences in information reported across different studies and surveillance systems. In some systems, clinically diagnosed pertussis cases (without laboratory confirmation) are reported, while other systems focus on laboratory-diagnosed pertussis. In systems that gather clinically diagnosed pertussis reports, there is potential for overestimating pertussis disease rates. In contrast, other systems that focus on laboratory-confirmed pertussis reports may underestimate true pertussis rates, because substantially less than 100% of clinically suspected pertussis may undergo laboratory testing (163). Underreporting of cases is more likely, and it has been suggested that the true incidence of pertussis is at least three times higher than the official reported rates (164–170). Underreporting is of particular significance with regard to older children and adults, for whom the cough pattern may be atypical. Clinical presentations with atypical cough may result in significant delays in seeking medical consultation (171–173).

For the past several decades, routine pertussis immunization has dramatically reduced disease incidence. In the past, pertussis was primarily a disease affecting children less than 6 years old. However, in the past 20 years there has been a change in the epidemiology of pertussis such that adolescent and adult pertussis

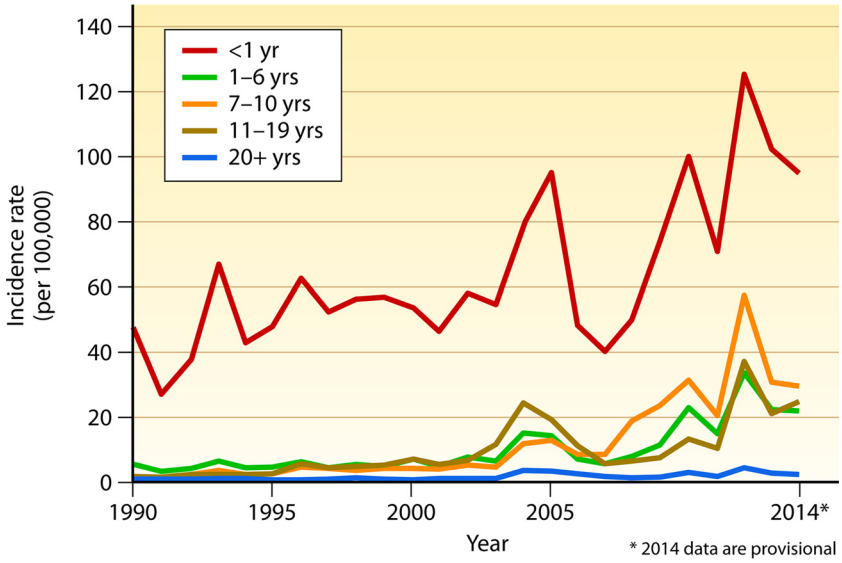

FIG 1 Incidence rates of pertussis by age group reported to the Centers for Disease Control and Prevention from 1990 to 2014. (Adapted from CDC National Notifiable Disease Surveillance System and Supplemental Pertussis Surveillance System [http://www.cdc.gov/pertussis/surv-reporting.html].)

continues to be a global concern, even in countries with relatively strong economies and high rates of childhood immunization, such as Australia, Belgium, Canada, Finland, France, Germany, Italy, Japan, The Netherlands, Spain, Switzerland, the United Kingdom, and the United States (174–187).

Burden of Pertussis in Infants and Toddlers

In the vaccine era (from the 1940s to the present), pertussis epidemics have occurred in 3- to 4-year cycles that may have resulted from the cycling of population immunity (188, 189). In the United States, pertussis has become endemic and is currently considered the most common vaccine-preventable disease (190–195). Recent nationwide incidences of pertussis for children less than 6 months, 6 through 11 months, 1 through 6 years, and 7 through 10 years were approximately 160, 40, 22, and 30 per 100,000 population, respectively (196). In 1994 to 1998, ~13,800 children less than 2 years old were hospitalized as result of pertussis, whereas in 1999 to 2003, the number of hospitalizations was ~17,000 for the same age group (197). In 2003, 19% of total reported pertussis cases (n = 11,647) occurred in infants aged less than 1 year (198). In 2010, a total of 25 deaths were reported among infants aged less than 6 months (199). In the United States, from 2012 to 2013, 12 pertussis-associated deaths were reported in infants under 3 months of age, and one child died among children aged 1 through 4 years old (200). From 2013 to 2014, seven deaths in infants under 3 months old and one fatality in children 1 through 4 years old were reported (196). Figure 1 shows the reported pertussis incidence by age group from 1990 to 2014.

Pertussis outbreaks have occurred in several states and in all regions of the United States (201–206). In Ohio, from 2009 through 2010, 2,958 cases were reported (205). Additionally, from May 2010 through May 2011, a mixed pertussis and pertussis-like illness outbreak produced 918 cases in Franklin County, Ohio (34). In 2012, Minnesota experienced a large pertussis epidemic in which 4,144 cases were reported (206). Nationwide, during 2012, the total number of reported pertussis cases in all age groups exceeded 48,000, including 20 pertussis-related deaths that occurred primarily in infants aged less than 3 months (207). From 2012 through 2014, 6,231 cases were reported from Washington State. In 2012 alone, a majority (31 of 39) of Washington State counties were affected. In the same year (2012), there were 4,918 total cases (including both confirmed and probable cases), with an overall incidence of 11/100,000 residents (203, 208). During this outbreak, 95 infants were diagnosed with pertussis (incidence, 107/100,000), including 35 children who required hospitalization (208). In 2013 and 2014, while transmission continued, the number of reported pertussis cases declined to 748 and 565 cases, respectively (202, 208). However, in 2015, the number of pertussis cases reported to the Washington State health department through week 48 exceeded 1,300, compared with 456 reported cases through week 48 in 2014 (202). In Michigan, the number of cases reported from 2010 through 2012 exceeded 3,000, with more than half (n = 1,564) of these cases reported in 2010 (204).

From 2010 through 2014, pertussis has been widespread throughout the state of California; 26,566 cases were reported, more than 1,700 of the patients were hospitalized, and there were 15 reported fatalities. In 2014, the number of cases reported (n = 10,831) was the highest of any single year (201). Among them, 376 people were hospitalized, and 85 (23%) of them required intensive care. Of the 376 hospitalized patients, 227 (60%) were infants less than 4 months of age, and four cases were fatal in infants less than 2 months of age. The cumulative pertussis disease burden in California from 2010 to 2014 underscores the ongoing impact of pertussis.

Recently, Canadian public health officials identified an outbreak of pertussis that began in the Mauricie-Central Quebec region during early October 2015 (209). This outbreak resulted in 151 pertussis cases identified from approximately 12 elementary schools, 2 high schools, and more than 10 day care centers. In 2015, other areas of Canada experienced pertussis outbreaks, including Manitoba, where 51 pertussis cases were reported and the vast majority of those cases were among infants, children, and adults who were unimmunized. In addition, New Brunswick,

Canada, reported an outbreak of 56 confirmed pertussis cases. British Columbia, Canada, also reported high numbers of pertussis cases with twice as many cases reported in 2015 as in 2012.

Severe pertussis cases resulting in death have occurred in populations that suffer from health disparities. In 2003, Vitek and colleagues reported pertussis-associated mortality among infants in the United States (210). They found that pertussis-associated deaths were at least 2.6 times higher in Hispanic infants than in non-Hispanic infants during the 1990s. In another study, Murphy et al. investigated the impact of pertussis in American Indian and Alaska native infants from 1980 to 2004 (211). Murphy and colleagues found nearly 500 pertussis-associated hospitalizations among Native American and Alaskan infants, with an annual hospitalization rate of 133 per 100,000 infants. In 2002 to 2004, Murphy et al. estimated that hospitalizations among Native American and Alaskan infants far exceeded those found among the general U.S. infant population (101 per 100,000 versus 68 per 100,000). A number of important factors may explain the higher pertussis burden found in Native Americans, including lower immunization rates than in other populations, the absence of a medical home, and suboptimal living (e.g., household crowding) and socioeconomic conditions that favor pertussis transmission (212–214).

Burden of Pertussis in Adolescents and Adults

Pertussis among adolescents and adults has been reported with increasing frequency during the last 2 to 3 decades (188, 190, 215–233). Population-based studies between 1991 and 1999 estimated an incidence of pertussis in adults of 133 to 507 per 100,000 person-years (167, 171, 234–237), which equates to more than one million cases of pertussis among adults in North America annually (167). In 2013, the nationwide incidences of pertussis among persons 11 to 19 years old and 20 years or older were approximately 28 and 21 per 100,000, respectively (200). Although limited published data exist to describe vaccine uptake coverage stratified by age, city, or state, state-by-state variations in the distribution of pertussis among adolescents and adults have been observed. For example, for 10 years (1989 to 1998), there was an increase in the incidence of pertussis in Massachusetts, where by 1998, 92% of cases reported were among adolescents and adults. In comparison, nationwide, only 47% of cases reported were in this age group (238). In the 2014 pertussis outbreak in California, most reported cases were among adolescents aged 9 to 16 years, and whites were more affected than other racial/ethnic groups (201). The observed increase in reported cases among adolescents and adults has been attributed, in part, to waning immunity that occurs several years after primary childhood immunization (216, 239–246). Such waning immunity likely plays an important role in pertussis transmission among household contacts (218, 247–253).

Seasonality

Unlike the case for other respiratory pathogens, *B. pertussis*-associated outbreaks do not uniformly show a distinct seasonality. North American studies have shown a predominance of endemic cases during the autumn and winter. In a retrospective study examining pertussis incidence over a 13-year period with over 2,500 confirmed pertussis cases in Toronto, Canada (most [78.4%] were children under 15 years of age), investigators found an autumn and winter seasonal predominance (254). In British Columbia, Canada, Skowronski et al. demonstrated a peak of pertussis among adolescents during August and September 2000 in a population-based study (231). In a recent pertussis outbreak in rural Texas, 34 cases were reported (23 were confirmed and 11 were epidemiologically linked); the first case was reported in late October 2012 (194).

However, in other studies, seasonality of pertussis was not consistent in time or place (181, 255, 256). From 1996 to 2006 in The Netherlands, investigators reported an August peak incidence of pertussis among infants and young children and another peak in November among adolescents (256). Fine and Clarkson described the seasonal pattern of pertussis in England over several decades (255). From 1940 to 1957, peaks of pertussis epidemics were noted in the early or middle months of the year. Between 1958 and 1975, pertussis epidemic peaks were observed predominantly in October through December of each year. For the decade from 1976 through 1985, a bimodal pattern of seasonality (peaks in September and February) was observed. Although studies of pertussis seasonality to date have come largely from countries with temperate climates, limited data are available from tropical/subtropical areas (257). In Senegal, like The Netherlands and England, pertussis has demonstrated a bimodal peak of transmission in some years, with smaller peaks of disease in summer months followed by large epidemic seasons in winter months (258). In Kenya, epidemiological surveillance data from 1974 through 1981 showed a distinct winter seasonality with two pronounced epidemic years (259). In developed and developing countries, climatic factors such as temperature and humidity may play an important role in transmission. In addition, in more developed populations, other factors, such as day care attendance, may act as important drivers for pertussis transmission and seasonal patterns.

Transmission Dynamics of Pertussis

Pertussis is highly contagious and can spread rapidly from person-to-person through contact with airborne droplets. The human nasopharynx can be densely colonized with both commensal bacteria and pathogens, including *B. pertussis*. Infected individuals aerosolize pertussis-containing droplets by coughing or sneezing (260). Studies of infectious disease transmission estimated the basic reproductive number (R_0) for various infectious diseases, including pertussis. R_0 is defined as the expected number of secondary cases produced by a confirmed primary case in a completely susceptible population (261). Based on R_0 estimates, pertussis is considered far more contagious than polio, smallpox, rubella, mumps, and diphtheria (262, 263). Studies showed that one infected person can transmit *B. pertussis* to as many as 12 to 17 other susceptible individuals, while R_0 values for polio and smallpox (5 to 7), rubella (6 to 7), mumps (4 to 7), and diphtheria (6 to 7) are substantially lower (261–266). Kretzschmar et al. found that the R_0 for pertussis across five European countries (Finland, Germany, Italy, The Netherlands, and the United Kingdom) during the 1990s was approximately 5.5, which is lower than R_0 estimates in previous studies (267). Moreover, in a recent systematic review, it was estimated that the mean interval from symptom onset in a primary pertussis case to symptom onset in a secondary case is 22.8 days (268). Similarly, the secondary attack rate is estimated to be at least 80% (171, 269, 270).

As in many other countries, the United States had experienced a decline in reported pertussis since the introduction of pertussis vaccines. Nevertheless, a nationwide reemergence of pertussis occurred and continued. In 2011, Rohani and Drake analyzed per-

tussis notifications in the United States in the period from 1951 to 2010 (271). For this analysis, data were obtained from the National Notifiable Disease Surveillance System, and the goal of the study was to explore the timing, spatial pattern, and consistency of resurgence across the country. Their results showed that a pertussis resurgence occurred at different times in different states, spread out over a transition period of nearly 30 years. Despite this spatial variation, broad patterns in pertussis epidemiology can be summarized as two dominant phases: a period of decline ending in the mid-1970s, followed by nationwide resurgence. The causes of these fluctuations in the epidemiology of pertussis are still a topic of controversy, though the findings of Rohani and Drake (271) suggest that evolution of the *B. pertussis* bacterium, loss of immunity and persistent transmission among adults, availability of better diagnostics (PCR), and demographic drivers are more probable explanations than changes in reporting or the switch from whole-cell to acellular pertussis vaccines. Another key factor that may play a role in the observed resurgence is the rise of pockets of underimmunization, leading to a build-up of susceptibility from which outbreaks arise. In addition, variable immune responses among target groups for tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) immunization (i.e., pregnant women and adolescents) may translate into some individuals experiencing waning of protective levels of antibody over time.

Economic Impact of Pertussis

B. pertussis infection can lead to severe disease in adults, resulting in lost work time, clinic or emergency department visits, or hospitalization (226, 238, 272–275). Consequently, the direct and indirect pertussis-related costs are high. Lee et al. estimated total societal costs (medical and nonmedical costs) related to pertussis to be approximately $800 and $1,950 per case in adolescents and adults, respectively (275). In that study, the medical cost related to health service utilization (i.e., number of physician visits, antibiotic treatment, laboratory tests, chest radiograph, and hospitalization) was approximately $240 per case among adolescents and $330 among adults. These medical costs per case would double if postexposure prophylaxis (PEP) for close contacts had been included in the analysis. The average nonmedical cost per case (i.e., days missed from work for adult patients and parents of children, or from school, and other out-of-pocket costs such as those for transportation to doctor visits, for babysitting, and for over-the-counter medications) was estimated to be $155 for adolescents and $447 for adults. Unit costs for services were based on reimbursement rates from the Medicare Fee Schedule and the Physician Fee Schedule (275). In a family-based study, Lee and Pichichero estimated the costs of pertussis for 87 individuals in 69 households (276). They found that the average medical cost for an infant, child, adolescent, and adult was approximately $2800, $300, $250, and $180, respectively. Parents lost an average of six work days to care for an ill child; for these parents, costs associated with work loss averaged $767 per family. Even for parents who did attempt to work while a family member suffered from pertussis, nearly 60% reported decreased work productivity, ranging from 25% to 99%. In that study, work-related costs contributed more than 60% of the overall costs of pertussis (276).

TABLE 3 Clinical manifestations of pertussis among infants, children, adolescents, and adults, 1988 to 2002

Clinical sign (reference[s])	Frequency (%) in:	
	Infants and children[a]	Adolescents and adults
Coughing paroxysms (167, 219, 226, 234, 273)	89–93	70–99
Inspiratory whoops (167, 219, 224, 226, 234, 273, 289, 659,)	69–92	8–82
Nocturnal cough (219, 224, 226, 232, 660)	41	61–87
Posttussive vomiting (167, 219, 224, 226, 232, 234, 273, 289, 659)	48–60	17–65
No or low-grade fever (234, 659)	87–96	13
Coryza (234)	NA[b]	58
Pharyngitis (234)	NA	31

[a] Ages 6 days to 9 years.
[b] NA, data not available.

CLINICAL PRESENTATION

In patients infected with *B. pertussis*, the incubation period usually lasts 7 to 10 days, but incubation periods as long as 4 weeks have been observed (277). Although pertussis most often presents clinically as whooping cough, the range of signs and symptoms at presentation can vary from the youngest infants to adolescents (Table 3). Infants and children manifest a range of symptoms from asymptomatic or mild upper respiratory tract disease to severe, persistent, and progressive coughing that continues for weeks or months. The classic symptom of pertussis, from which the original name "whooping cough" is derived, consists of violent and rapid coughing with rapid expulsion of air from the lungs, in which the patient is then forced to inhale with a loud "whooping" sound. In infants and young children, the clinical course of pertussis progresses through three consecutive stages after infection and incubation: the catarrhal, paroxysmal, and convalescent stages. Each stage lasts approximately 1 to 3 weeks, and the patients typically do not fully recover for 2 to 3 months (155, 272, 278, 279).

In the first stage, the catarrhal stage, infants and children often present with normal body temperature or low-grade fever, malaise, sore throat, nasal congestion, rhinorrhea, lacrimation, sneezing, and mild progressive dry cough. Although coryza, pharyngitis, and nocturnal cough paroxysms are commonly reported, there are limited systematically collected data for these signs. In the catarrhal stage, the diagnosis of pertussis is frequently overlooked by clinicians because these signs and symptoms mimic those in other viral infections associated with rhinoviruses, coronaviruses, and influenza viruses and perhaps because they expect the vaccinated child to be protected from pertussis infection (280, 281). At this stage of illness, parents frequently bring children to ambulatory care clinics and emergency departments. In these outpatient settings, clinicians need to maintain a high index of suspicion for pertussis in order to provide appropriate referrals to nearby health facilities that are equipped to deliver emergency supportive care and confirmatory diagnostic testing for pertussis. Delays in diagnosis and treatment of pertussis facilitate its transmission to household contacts, friends, schoolmates, and family members (145, 233, 282).

In the second stage of illness, the paroxysmal stage, patients

experience bouts of intense and violent coughing (5 to 10 coughs/paroxysms) that last several minutes and are associated with cyanosis, eye proptosis, tongue protrusion, salivation, thick oral mucus production, lacrimation, and engorgement of neck veins (163). The classic sign of pertussis, the inspiratory whoops, manifests at this stage (283). Coughing paroxysms may result from the effects of toxin or from the hardening of mucus that becomes difficult to dislodge from the trachea, bronchi, or bronchioles. Paroxysms can be triggered by stimuli such as crying, laughing, and eating (284). Such paroxysms often occur at night and increase in frequency during the first 1 to 2 weeks of this stage through weeks 2 to 3, with a gradual decline thereafter. In the paroxysmal stage, patients might also experience vomiting (post-tussive vomiting), fatigue, and respiratory exhaustion.

In the third stage, convalescence, coughing paroxysms recede in frequency, duration, and severity. However, a mild, chronic, nonparoxysmal cough can last up to 6 weeks. In children who have had the classic type of pertussis, cough paroxysm patterns can recur if the child contracts another viral infection (145, 272, 278). By this stage, patients will have already received appropriate antibiotic and supportive therapy.

Adolescents and adults present with signs and symptoms similar to those in infants and children. In general, however, most adolescents and adults have symptoms that are milder than those of infants and children; consequently, pertussis in adolescents and adults can escape detection by clinicians (233, 285–287). Although classic pertussis presentation can still occur in many patients, pertussis without the classic paroxysms is the cause of up to one-third of illnesses with prolonged cough in this age group (219, 288). Therefore, pertussis should be highly suspected as a cause of cough that persists for more than 3 weeks, regardless of whether it is paroxysmal (288). In adolescents and adults, cough duration ranges from 3 to 8 weeks (167, 217, 219, 232, 273, 289). Studies suggested that the clinical presentation of pertussis is influenced by age, gender, infecting species (e.g., *B. pertussis* versus *B. parapertussis*), infectious dose, and time from last pertussis vaccination (144, 145, 218, 290). Symptomatic reinfections are common in adolescents and adults (273, 291). In a pertussis vaccine efficacy trial of 246 adults conducted between 1991 and 1994, 64 subjects were identified with clinical and laboratory-confirmed pertussis, of whom 26% had a history of pertussis infection (234). In older adults, the classic whooping cough can be dramatic, as demonstrated by a recent case study of pertussis in a hospitalized adult (292). Also, in older adults, the clinical presentation of pertussis might be influenced by preexisting immunity to *B. pertussis* as a result of previous exposure or immunization. Adults who had been recently immunized or had a previous pertussis infection tended to have less dramatic presentation, particularly those lacking comorbid medical conditions (144, 145, 218, 290).

COMPLICATIONS OF PERTUSSIS IN INFANTS, CHILDREN, AND ADULTS

In patients of all ages, delayed clinical recognition of pertussis is more likely to result in clinical complications and sequelae (Table 4). Overall, young infants are at highest risk for severe outcomes, such as respiratory failure and death (189, 191, 278, 280, 290, 293–311). In the United States, it has been estimated that more than half of infants infected with pertussis require hospitalization, and about one in 100 infants die as a result of pertussis (272, 312). Infants hospitalized for pertussis have been shown to present with apnea, pneumonia, and convulsions (313). In a study conducted in California, among 17 infants less than 3 months of age who were admitted to pediatric intensive care units with severe pertussis, six infants were diagnosed with pulmonary hypertension and four of those six died (314).

TABLE 4 Clinical complications of pertussis among infants, adolescents, and adults, 1981 to 2015

Complication (reference[s])	Frequency (%) in:	
	Infants	Adolescents and adults
Apnea (312, 313, 326, 327)	50–67	27–86
Pneumonia (273, 312, 313, 326, 327)	20–23	0.6–8
Convulsions (313, 326, 327)	1	0–0.6
Death (190, 312, 313, 661)	1–1.6	0.01
Insomnia (326)	NA[a]	77
Sinusitis (273)	NA	13
Otitis media (273, 329)	6	4
Weight loss (273, 313, 326, 329)	12	3–33
Urinary incontinence (273, 312, 313, 326)	NA	3–28
Syncope (273, 312, 313, 662)	NA	2–6
Rib fracture (273, 312, 313, 326, 327)	NA	1–4
Loss of consciousness (326)	NA	1
Hospitalization (312, 326, 327)	~50	0–12

[a] NA, data not available.

In infants and young children, pertussis can be accompanied by coinfection with other respiratory pathogens, particularly respiratory syncytial virus (RSV) (315). In one study, RSV was detected as a coinfection in 33% (11/33) of infants admitted for pertussis to either pediatric intensive care units or general pediatrics wards in London hospitals (251). In 2014, one research team found viral coinfections in 11 of 14 confirmed cases and in six of seven suspected cases of pertussis (316). In that study, influenza A virus, RSV B, rhinovirus, and bocavirus were the most common pathogens found. In several other studies, adenoviruses were isolated from children with pertussis (317–320). Coinfection with multiple or mixed pathogens, including bacterial and viral pathogens, has been reported in pertussis patients. In some cases, pertussis infection may be followed by synergistic superimposed bacterial and viral infections. These coinfecting pathogens include parainfluenza virus, RSV, *Mycoplasma pneumoniae*, adenovirus, and influenza A and B viruses (317, 320–323). Selected reports also identified *B. pertussis* coinfections with helminthic and parasitic pathogens, including *Plasmodium falciparum* and *Fasciola hepatica* (324, 325). However, rhinovirus and adenovirus may be found to colonize the upper respiratory tract in asymptomatic infants and children.

In adults, the complications of pertussis most commonly include insomnia, apnea, weight loss, urinary incontinence, syncope, and rib fracture. Less common manifestations include pneumonia, otitis media, and, rarely, death (190, 273, 312, 313, 326, 327, 329). Up to 12% of adults with pertussis require hospitalization (327). From 1990 to 2004, five pertussis-associated deaths in adults were reported to the U.S. Centers for Disease Control and Prevention (CDC) (327). Although reported deaths are infrequent (possibly due to underascertainment), these adults (aged 49 to 82 years) suffered from comorbid conditions, including diabetes, multiple sclerosis with asthma, multiple myeloma (requiring immunosuppressive therapy), myelofibrosis, and

TABLE 5 Antimicrobial agents for treatment and postexposure prophylaxis for *B. pertussis* infection, 1997 to 2013[a]

Agent (reference[s])	Age group	Dosing information	Comments
Erythromycin (220, 278, 332, 336, 344–346, 663)	>1 mo	40–60 mg/kg/day in 3 or 4 divided doses for 7–14 days	Drug-drug interaction with those metabolized by cytochrome P450; poorly tolerated (e.g., GI upset, hypersensitivity reactions, cholestatic hepatitis, sensorineural hearing loss)
	Adults	500 mg every 6 or 8 h for 7–14 days	Increased risk of IHPS in neonates; FDA pregnancy category B drug
Azithromycin (220, 278, 332, 336, 337)	<6 mo	10 mg/kg daily for 5 days	Well tolerated but GI upset can still occur; Drug-drug interaction with those metabolized by cytochrome P450
	≥6 mo	10 mg/kg on day 1, followed by 5 mg/kg on days 2–5	Administer 1 h before or 2 h after food and antacids
	Adults	500 mg on day 1, followed by 250 mg on days 2–5	FDA pregnancy category B drug
Clarithromycin (220, 278, 332, 337)	>1 mo	15 mg/kg/day in 2 divided doses for 7 days	Moderately tolerated (GI upset is common)
	Adults	500 mg every 12 h for 7 days	Drug-drug interaction with those metabolized by cytochrome P450; FDA pregnancy category C drug
TMP-SMZ (278)	>2 mo	TMP at 8 mg/kg/day plus SMZ at 40 mg/kg/day every 12 h for 14 days	Second-line treatment for those who have macrolide resistance or intolerance; FDA pregnancy category C drug
	Adults	TMP at 320 mg/day plus SMZ at 1,600 mg/day every 12 h for 14 days	Contraindicated in pregnant women and breastfeeding mothers

[a] GI, gastrointestinal; FDA, Food and Drug Administration; IHPS, infantile hypertrophic pyloric stenosis; TMP-SMZ, trimethoprim-sulfamethoxazole (co-trimoxazole).

chronic obstructive pulmonary disease. In 1998, De Serres et al. reviewed clinical pertussis cases in 280 adolescents and 384 adults who were seen in five public health units in Quebec, Canada (273). They found complications such as sinusitis, pneumonia, otitis media, urinary incontinence, weight loss, rib fracture, and syncope. Six percent of adults who were aged 50 years and older were hospitalized (mean length of stay, 17 days). In this Quebec study, 18% of all adult patients reported previous pertussis infection. Older adults with pertussis have also had uncommon nonrespiratory complications, including encephalopathy, intracranial hemorrhage, stroke, carotid artery dissection, pneumomediastinum, and herniated lumbar discs (313, 326, 330, 331).

POSTEXPOSURE PROPHYLAXIS AND THERAPEUTICS

The selection of antimicrobial agent should be driven based on the following considerations: age of the patient, drug-related adverse events or interactions, tolerability, medication regimen adherence, and cost. A limited number of antibiotic agents are available for pertussis management, including PEP in individuals who come in contact with clinical cases of pertussis. Close contacts include household members, caretakers, health care workers (HCWs), or any person who has had face-to-face exposure within three to four feet of a symptomatic patient or has shared confined space for 1 h or more or has had direct contact with the respiratory, oral, or nasal secretions of a symptomatic pertussis patient. PEP is recommended for all close contacts regardless of vaccination status (278, 332–335). The decision to administer PEP is based on many factors, including the severity of disease, duration and burden of exposure, and immunocompetence of the exposed contact (278).

The usefulness of antimicrobials to treat pertussis when given late in the course of disease is controversial, because the role of therapy is to lessen pertussis disease severity and duration. The use of antimicrobial therapy late in the course of disease is less likely to prevent pertussis symptoms than use early in the course of disease (278). Antimicrobial agents are recommended to clear the nasopharynx of *B. pertussis* and to prevent the spread of the infection (332, 336, 337). It was estimated that 80% to 90% of patients with untreated pertussis will clear *B. pertussis* from the nasopharynx within 3 to 4 weeks after the onset of cough (338). However, infants with pertussis who were not treated or vaccinated showed positive culture for more than 6 weeks (339). Table 5 summarizes groups of antimicrobials that have been used for pertussis treatment and PEP, along with recommended dosages across different age groups and potential adverse effects or contraindications. Neither the Clinical and Laboratory Standards Institute (CLSI) nor the European Committee on Susceptibility Testing (EUCAST) has established antimicrobial susceptibility cutoffs for treatment of *B. pertussis* (340, 341). Thus, clinical laboratories do not routinely perform susceptibility testing for antimicrobial agents used for *B. pertussis* treatment or PEP.

The effectiveness of antibiotic therapy depends on the stage of pertussis in which therapy is initiated. The first 3 weeks (catarrhal stage) are the optimal time for antibiotics to ameliorate the symptoms of pertussis and eradicate *B. pertussis*. Unfortunately, treatment is rarely given early enough to impact the course of the disease. For this reason, the U.S. CDC encourages clinicians to start antibiotic treatment based on their clinical judgment and even before laboratory results are known (342). No proven treatments exist that reduce disease severity and frequency of symptoms during the paroxysmal and convalescent stages of the disease (343). However, antimicrobials are still recommended to reduce *B. pertussis* transmission and to render patients noninfectious (272).

Macrolide antibiotics (e.g., erythromycin, clarithromycin, or azithromycin) have been effective and constitute the mainstay of treatment for patients with pertussis as well as for PEP (278). Although erythromycin has been recommended for treatment of pertussis or PEP, undesirable adverse events have led to poor med-

ication adherence and an increase in prescribing of newer macrolides (i.e., clarithromycin and azithromycin) (278). A relatively long duration of treatment or PEP (i.e., two completed weeks) has been suggested to prevent relapse (278). In 2007, Altunaiji et al. conducted a Cochrane review of 13 clinical trials, which involved more than 2,000 participants, to assess the risks and benefits of antimicrobial treatment of, and PEP against, whooping cough in children and adults (332). They found that short-term antibiotics (azithromycin for 3 to 5 days or clarithromycin or erythromycin for 7 days) were as effective as long-term erythromycin (for 10 to 14 days) to eradicate *B. pertussis* from the nasopharynx.

Among the three most widely prescribed macrolides, azithromycin is the only recommended antimicrobial for neonates (<1 month old) (278). Erythromycin has been linked with infantile hypertrophic pyloric stenosis (IHPS) in neonates, including those indirectly receiving erythromycin through breast milk (278, 344, 345). In one cohort study, infants receiving erythromycin prophylaxis were found to have greater risk of IHPS (7/157 among those exposed versus 0/125 among those with no erythromycin exposure) (278). In a large retrospective study, Mahon et al. evaluated 14,876 infants treated with erythromycin (oral or ophthalmic administration) as well as mothers who received erythromycin during the third trimester to evaluate the risk of IHPS (346). Young infants (especially those less than 2 weeks of age) who received systemic erythromycin had a higher risk of IHPS than those given ophthalmic erythromycin. No clear association was observed among mothers who received macrolides and IHPS. More recently, in 2014, Danish investigators found an increased risk of IHPS when macrolides were used to treat young infants or when mothers used macrolides within the first 2 weeks after birth (347).

Although azithromycin is recommended for neonates because it is well tolerated and has a high safety profile (278), there may be an association between azithromycin and IHPS. In 2007, Morrison described 7-week-old premature triplets who were hospitalized because of clinical manifestations that were consistent with pertussis (348). All had been treated with azithromycin. Two of the infants were subsequently diagnosed with IHPS and treated surgically.

For children and adults, azithromycin, clarithromycin, or erythromycin may be used (278, 342). Azithromycin and clarithromycin allow for less frequent dosing, which typically results in better adherence to therapy. In addition, azithromycin has a very limited or no effect on the cytochrome P450 system, and more drug-drug interactions are expected with erythromycin and clarithromycin, where they can both inhibit cytochrome P450 (349).

Nonmacrolide Treatments

Trimethoprim-sulfamethoxazole (also known as co-trimoxazole) is used as an alternative to macrolides but should be used only in children older than 1 month and in adults when macrolides are not well tolerated (278). Because of the potential risk for kernicterus among infants, co-trimoxazole should not be administered to pregnant women, nursing mothers, or infants aged less than 2 months (278).

Ampicillin, cephalosporin, tetracycline, chloramphenicol, and fluoroquinolones have not demonstrated acceptable effectiveness in treating pertussis among infants, children, and adults. Furthermore, tetracyclines, chloramphenicol, and fluoroquinolones have potentially harmful side effects in children (350–352). Therefore, none of these antimicrobial agents is recommended for treatment or PEP of pertussis (278). Little is known about the effectiveness of antimicrobial therapy to treat *B. parapertussis* or *B. holmesii*, but some *in vitro* data suggest that macrolides would be effective (353).

Treatment of pertussis symptoms using corticosteroids (354–357), bronchodilators (355, 358–360), antitussives, antitoxin (pertussis immunoglobulin) (361, 362), or antihistamines (360, 363) has not been adequately evaluated. Thus, these therapeutics are not generally recommended.

Exchange transfusion for severe cases of pertussis, however, showed potential therapeutic benefit and promising results, particularly when applied early in the disease course. Infants with severe pertussis usually present with hyperleukocytosis and develop refractory hypoxemia and pulmonary hypertension that is unresponsive to maximal intensive care (364). This may reflect a hyperviscosity syndrome from the elevated WBC count. Several case reports suggested improved outcomes using exchange transfusion to reduce the WBC count (151, 306, 364–370).

Antimicrobial Resistance

Antimicrobial resistance to *B. pertussis* has been reported sporadically over 2 decades (351). It has been estimated that the occurrence of *B. pertussis* resistance to macrolides is less than one percent (371). Fry et al. proposed that the mechanism of resistance is due to a mutation of the erythromycin binding site in 23S rRNA (372).

In May 1994 in Yuma County, Arizona, susceptibility testing for *Bordetella* species was introduced (373). Among 70 pertussis cases reported to the U.S. CDC from Arizona, a highly erythromycin-resistant *B. pertussis* strain was recovered from a 2-month-old infant (374). The MIC for this drug-resistant isolate was >64 μg/ml; the normal range of MIC for erythromycin against *B. pertussis* is 0.02 to 0.1 μg/ml (351, 374). In a study of 47 *B. pertussis* strains isolated at the Primary Children's Medical Center in Salt Lake City, UT (1985 to 1997), one erythromycin-resistant isolate had an MIC of 32 μg/ml (375).

In Australia between 1971 and 2006, 99 isolates of *B. pertussis* and five isolates of *B. parapertussis* were collected. None of the *B. pertussis* isolates was erythromycin resistant, but all five isolates of *B. parapertussis* were found to have significantly reduced susceptibility to erythromycin and azithromycin (376). In the United Kingdom between 2001 and 2009, no *B. pertussis* resistance to erythromycin, clarithromycin, or azithromycin was found among 583 isolates tested (372). In 2012, Minnesota experienced the largest pertussis outbreak since 1940 (206). In that epidemic, 265 isolates were collected, and none of the isolates was macrolide resistant (377).

Since the introduction of macrolides as the first line of treatment for pertussis through 2012, only seven erythromycin-resistant isolates have been reported worldwide (373, 375, 378–381). Five of those resistant isolates were identified in the Unites States, with one each from Arizona, California, Georgia, Minnesota, and Utah. One case of erythromycin resistance was reported from Taiwan and one from France. Despite the infrequency of drug-resistant pertussis strains identified to date, continued surveillance of pertussis remains a high priority, in part to maintain vigilance for the emergence of drug resistance in *B. pertussis* (375, 378). Unfortunately, widespread use of PCR for pertussis diagnosis has led to markedly fewer cultures being obtained for pertussis diagnosis,

which has resulted in a lack of data on antimicrobial susceptibility of *B. pertussis* (376).

Other *Bordetella* species, such as *B. parapertussis*, *B. holmesii*, and B. *bronchiseptica*, can be treated with macrolides, but resistant strains of *B. parapertussis* and B. *bronchiseptica* have been reported (145, 382). Although macrolide-resistant strains are uncommon in many countries and the current therapeutic guidelines are appropriate, screening for antimicrobial resistance is still needed for surveillance and in settings where there is evidence of macrolide failure (372, 376).

IMMUNITY TO PERTUSSIS

Immunity to pertussis, acquired either from natural infection or through vaccination, is not lifelong. It has been estimated that natural pertussis infection yields 3.5 to 30 years of protection (383–386); the estimated protection obtained from the whole-cell pertussis vaccine is 5 to 14 years (387–393), and that from the acellular vaccine is 4 to 7 years (241, 390, 394–397). As a result of waning immunity over time, adolescents and adults are susceptible to infection with *B. pertussis*. The severity of their disease appears to be strongly linked to the time since previous vaccination or illness due to *B. pertussis* (215, 398).

Worldwide, it has been observed that many adolescent and adult patients with confirmed pertussis had a history of pertussis vaccination, had contracted pertussis during early childhood, or both (218, 399, 400). In 2006, Ward et al. conducted a double-blind randomized clinical trial to assess the rates of *B. pertussis* infection among adolescents and adults (401). In the control group, which did not receive acellular pertussis vaccine (~1,390 participants), 0.4% to 2.7% showed evidence of pertussis infection during 11 months of follow-up. *B. pertussis* infection was based on immunoglobulin G (IgG) or immunoglobulin A (IgA) antibodies to PT, PRN, FHA, and FIM. Two percent of nonvaccinated participants had 4-fold-higher antibody titers for one of the following *B. pertussis* virulence factors: PT, pertactin, FHA, FIM, PT plus any other antibody, pertactin plus PT, pertactin plus FIM, or FHA plus FIM. They concluded that asymptomatic infection was approximately five times more common than reported. In 2010, to estimate the incidence of pertussis, Kretzschmar et al. analyzed serological data from five European countries using two different approaches (267). The first approach consisted of cross-sectional surveys of IgG PT antibody titers combined with longitudinal information about the distribution of amplitude and decay rate of titers in a back-calculation approach. The second approach used age-dependent contact matrices and cross-sectional surveys of IgG PT to estimate a next-generation matrix for pertussis transmission among age groups. Using the first approach, the annual seroincidence of pertussis among adolescents and adults ranged from one to six percent, and when the second approach was used, the pertussis incidence ranged from one to four percent. Another seroepidemiological study was conducted in a highly vaccinated population (>93%) in Israel to estimate the magnitude of *B. pertussis* infections (402). Approximately 2,000 serum samples were analyzed using standardized methods for IgG PT. The estimated seroincidence rate was ~2,500 per 100,000 population (≥3 years of age) for the year 2000, compared to an incidence of reported pertussis of 5.6 per 100,000 for the same year, indicating that asymptomatic natural *B. pertussis* infection is far more common than clinical illness.

Vaccine-Induced Immunity

IgG or IgA enzyme-linked immunosorbent assays (ELISAs) were used to measure antibody to PT, FHA, PRN, or FIM in acellular pertussis vaccine trials involving adolescents and adults (236, 403–405). In 2000, Van der Wielen et al. tested the immunogenicity and safety of acellular pertussis vaccines in 299 adults (403). Prior to vaccination, baseline IgG antibody titers to PT, FHA, and PRN were 73.1%, 98.2%, and 74.5%, respectively. One month after vaccine administration, the IgG titers to PT, FHA, and PRN were 96.8%, 100%, and 98.9%, respectively. In 2007, Guiso et al. conducted a serological follow-up study to assess humoral and cell-mediated immunity in children who had received primary and booster vaccination with either the whole-cell pertussis vaccine or the three-component acellular pertussis vaccine (PT, FHA, and PRN) (406). In this study, for both groups, 3- and 6-year serological and cell-mediated immunity follow-up was performed after a booster dose of either vaccine in the second year of life. At 6 years of follow-up, there was a significant difference in seropositivity between the two groups, in which the anti-PRN IgG level was higher in the acellular vaccine group (95.1%) than in the whole-cell vaccine group (66.7%). The stimulation index (SI) range was also compared: at 3 years of follow-up, the percentage of children with positive cell-mediated immunity (SI ≥ 3) was higher for all three antigens in the acellular pertussis vaccine group. At 6 years of follow-up, the SI was still higher for two antigens (FHA and PT) in the acellular pertussis vaccine group. No difference between groups was detected for PRN. The investigators concluded that the protection provided by three-component acellular pertussis vaccines was as good as that provided by efficacious whole-cell pertussis vaccines.

Immunological studies from the past 15 to 20 years suggest that cellular immunity has a fundamental role to play in the immune response for all pertussis-containing vaccines (whole-cell and acellular vaccines) (407–410). In particular, Toll-like receptor 4 (TLR4) in concert with CD4-positive type 1 T-helper cells (Th-1) and interleukin-17 (IL-17)-producing T-helper cells (Th-17) appear to play a central role in mediating protective immunity after whole-cell pertussis vaccination (408, 411), whereas Th-1 cells alone mediate the protective immune response after recovery from *B. pertussis* infection (409, 411). In infants, conventional whole-cell pertussis vaccines elicited a higher level of CD3 T-lymphocyte proliferation than did the low-lipopolysaccharide-content whole-cell vaccine (412). Other molecules playing a role in protection against pertussis include interferon gamma, which appears to protect against systemic dissemination (413), IL-12, which induces Th-1 cells (414), and tumor necrosis factor alpha (TNF-α), which enhances macrophage phagocytosis of *B. pertussis* (415).

In contrast, acellular pertussis vaccines appear to induce a predominantly Th-2 CD4-positive cellular immune response (408, 411, 416–418). However, in other studies, a Th-1 or a mixed Th-1/Th-2 response was also observed after three-component acellular pertussis vaccination (406, 411, 419–424). It has been demonstrated that the Th-2 immune response is not as effective as the Th-1/Th-17 response (425). Thus, the absence of a Th-1/Th-17 cellular immune response after immunization with acellular pertussis vaccines might explain the lower long-term protection of acellular vaccines (426). Other factors, noted in the foregoing section addressing changes in transmission dynamics for pertussis,

may also play a role in lower long-term acellular vaccine protection, including the buildup of susceptible individuals in pockets of underimmunization and variable immune responses in select groups such as pregnant women or adolescents. For this reason, the addition of a TLR4 ligand as an adjuvant has been suggested as a strategy to improve Th-1 and Th-17 responsiveness to acellular pertussis vaccination (193, 425, 426). Development of new acellular pertussis vaccines with multiple components or whole-cell pertussis vaccines with detoxified LPS has been suggested as options to enhance immunogenicity and safety (45).

In recent years, there has been an emerging controversy regarding the existence of herd immunity (herd protection) induced by acellular pertussis vaccines. Warfel et al. (427–429) argue that current acellular pertussis vaccines fail to prevent nasopharyngeal colonization and transmission of *B. pertussis*. To test this hypothesis, they vaccinated nonhuman primates (infant baboons) at 2, 4, and 6 months of age with acellular pertussis or whole-cell pertussis vaccine and challenged them with *B. pertussis* at 7 months of age. After infection, they quantified *B. pertussis* colonization in nasopharyngeal washes and monitored leukocytosis and pertussis symptoms. The investigators concluded that acellular pertussis vaccines protected against the development of clinical pertussis but did not protect against colonization and transmission of *B. pertussis* infection, indicating that herd immunity from acellular pertussis vaccines is doubtful.

Although the existence of herd protection induced by acellular pertussis vaccines has been challenged, population-based epidemiological surveillance for pertussis in Sweden following introduction of the acellular vaccine demonstrated herd protection among infants too young to receive a vaccine and older infants unvaccinated against pertussis (430). In addition, epidemiological modeling based on a model originally conceived by Rohani et al. suggests that achieving the observed reductions in pertussis would be impossible in the absence of herd protection (431, 432). For DTP vaccines, Jackson and Rohani demonstrated that herd protection can be achieved from DTP vaccines (433). They showed that the nationwide use of DTP vaccine in the routine immunization schedule over several decades had reduced the number of pertussis outbreaks in the United Kingdom. Moreover, the interval between pertussis outbreaks was prolonged, indicating that DTP vaccines prevented disease and reduced *B. pertussis* transmission. Although limited animal model data suggest that acellular vaccines do not produce herd protection, real-world epidemiological data in a large population as well as additional modeling data provide compelling evidence for herd protection. Additional studies to document herd protection in other infant and childhood immunization programs will be valuable to further quantify the extent of herd protection induced by acellular pertussis vaccines.

CONTROL MEASURES FOR PERTUSSIS OUTBREAKS

In several countries (particularly low- and middle-income countries), persistently low pertussis vaccine coverage has resulted in endemic levels of pertussis accompanied by large outbreaks. In the late 1990s, international health organizations, foundations, and bilateral aid agencies recognized that a global cooperation effort to strengthen immunization programs was needed. From this effort, the Global Alliance for Vaccines and Immunization (GAVI) emerged to become the leading international body to provide national immunization programs with access to funds that enable them to build an immunization infrastructure and improve pertussis (and other) vaccine coverage (434). Despite these efforts, the WHO released a global vaccination coverage report in 2014 indicating that third-dose coverage of diphtheria-tetanus-pertussis (DTP3) vaccine was less than 50% in several countries, including Chad, Central African Republic, Equatorial Guinea, Somalia, South Sudan, and Syria (159). Somewhat higher DTP3 vaccine coverage of 50% to 79% has been reported in Afghanistan, Benin, Democratic Republic of Congo, India, Madagascar, Mali, Myanmar, Nepal, Niger, Nigeria, Pakistan, Papua New Guinea, South Africa, Zambia, and Zimbabwe (159). Even as countries initiate new vaccine introduction to prevent pneumococcal diseases or rotavirus diarrhea, several countries need additional resources and/or technical assistant to achieve DTP3 coverage rates above 80%.

Pertussis outbreaks have been also reported in North America, Europe, and Australia (182, 195, 202, 203, 254, 264, 435–438). In contrast, few data are available from Latin American, Asian, and African countries compared with Europe and the United States (174, 439–446). In the United States, reported outbreaks that have been investigated by local and state health departments have affected diverse populations, including school children, military personnel, and hospitalized patients (245, 446–453). During the past decade, several pertussis outbreaks have been associated with pockets of underimmunization of children (454–456). With continued reports of pertussis outbreaks, there have been ongoing demands placed on city and state health departments to carry out timely outbreak investigations and implement effective control measures. Such control measures vary by country and jurisdiction due to differences in local immunization policies (457, 458). In the United States, control measures to limit the duration of a pertussis outbreak and reduce transmission in outbreak settings focus on providing PEP with antibiotics and ensuring that unvaccinated or undervaccinated individuals are appropriately covered (278, 333, 459, 460). For this purpose, the antibiotic of choice depends on a number of factors, including local drug availability, cost, and drug allergies (278).

In suspected pertussis outbreaks, control measures begin by first confirming pertussis among affected individuals. To confirm the illness, clinical specimens (e.g., nasopharyngeal swabs) are collected and tested. According to the U.S. CDC, diagnosis of pertussis in outbreak situations is best done by culture (333). Given the potential for false-positive results associated with PCR, the U.S. CDC advises exercising caution in using PCR during outbreak investigations. Pulsed-field gel electrophoresis (PFGE) is currently the most widely used method to track transmission patterns in an outbreak and characterize *B. pertussis* strains (462). Newer PFGE methods offer the potential for improved standardization and comparison of *B. pertussis* strains detected in different laboratories (333, 462). Recently, a new strain-typing technique called single nucleotide primer extension (SNPeX) was developed and showed promise as a flexible and time-efficient way to study outbreaks of *B. pertussis* and other pathogens (464). SNPeX analyzes fluorescently labeled DNA fragments with high-throughput capacity, a high degree of discrimination, and adaptability for detecting strains that may evolve and vary genetically within outbreaks or from one outbreak to another.

To facilitate the identification of cases in an outbreak, active surveillance must begin with systematic specimen collection and expedited transport of the specimens to laboratories that have the capacity to perform pertussis testing in a standardized fashion (e.g., state health laboratories). The U.S. CDC guidelines for the

control of pertussis outbreaks state that confirmation of the pertussis outbreak requires the presence of one or more culture-confirmed pertussis cases (333). Once the diagnosis of the index case(s) and etiology of the outbreak are confirmed, attention then focuses on identifying suspected cases and expanding testing to exposed individuals with suspected pertussis (333). Probable and confirmed cases should be reported rapidly; any delay in reporting will result in more secondary cases and more difficulty in containing the infection (333). Previous studies suggest that reporting delays, often seen during outbreaks, may facilitate pertussis transmission (465, 466). In 2004, Jajosky and Groseclose reviewed a few studies that described reporting timeliness in National Notifiable Disease Surveillance System data (466). They found that the median national reporting delay, based on date of disease onset, was 40 days for pertussis. Marinovic et al. developed a model to evaluate reporting timelines for several communicable diseases, including pertussis (467). They found that the delay in reporting should be reduced by at least 5 weeks to substantially reduce the spread of the infection.

In outbreak settings, ongoing communication with families, parents, schools, teachers, institutional administrators, hospitals, faith-based organizations, and local health departments is essential for efficient and effective outbreak control. Communication with and among these individuals and groups will facilitate ongoing identification of suspected cases of pertussis, and those individuals can be offered confirmatory laboratory testing. In addition, through contact with members of the community and community leaders, education to increase awareness of pertussis and its risk to members in the community can be disseminated through word of mouth, social media, radio, TV, and print media.

Vaccination and Prophylaxis for Outbreak Control

Current guidelines for DTaP immunization of infants and children as well as guidelines for the use of Tdap for older children, pregnant women, and adults provide important information on the use of pertussis-containing vaccines in populations affected by an outbreak (195, 333). Whenever possible, individual immunization histories should be reviewed to identify children who may need additional vaccines and adolescents or adults who may need their first or repeat doses of Tdap (468, 469). Recent guidelines for the use of Tdap in pregnant women suggest that all pregnant women should have immunization histories reviewed and vaccine offered to protect the mother at the time of delivery and to protect their babies after delivery (195, 242, 469, 470). In addition to providing pertussis vaccines to eligible individuals, PEP can be used to protect close contacts of confirmed or suspected pertussis cases. If possible, all household contacts of a pertussis case should receive PEP (278). The U.S. CDC recommends administration of PEP to asymptomatic household contacts within 21 days of onset of cough in the index patient (459). In determining the need for PEP, attention to persons with high-risk conditions (e.g., young infants, women in their third trimester of pregnancy, and those with preexisting health conditions) should lead to prompt evaluation by health professionals (459).

In health care institutions, reducing the potential for pertussis transmission can be achieved by reducing exposure to respiratory droplets from coughing or sneezing. For this reason, placement of patients with pertussis in a private room is advised. If no private rooms are available or if several patients have pertussis, then cohorting of pertussis patients is an option. Administration of post-exposure chemoprophylaxis to household contacts and HCWs who have had prolonged exposure to respiratory secretions is also recommended (471, 472).

VACCINES AND IMMUNIZATIONS

DTP and DTaP Vaccines for Infants and Young Children

Prior to the 1940s, in excess of 200,000 pertussis cases were reported in the United States annually. In 1934, the greatest number (n = 260,000) of annual cases was reported (473). In the United States, DTP vaccines were first licensed in 1914 and became available for routine infant immunization in 1948 (473). In 1976, the number of pertussis cases reported to the U.S. CDC reached its nadir at approximately 1,000 (144, 271, 474–476). In the United States, the whole-cell pertussis vaccine has been administered to children in combination with diphtheria and tetanus toxoids. Whole-cell pertussis vaccines, consisting of suspensions of inactivated *B. pertussis*, elicit humoral immunity to pertussis following intramuscular injection (477). Based on that concept, the first evidence of DTP vaccine efficacy was obtained from a clinical trial conducted during the 1929 pertussis outbreak in the Faroe Islands of Denmark (478, 479). In the 1930s, many steps were taken to improve DTP vaccines, including increasing the number of inactivated *B. pertussis* bacteria in the vaccine, standardizing the methods used to grow and kill the bacteria, and using fresh, rapidly growing phase one bacteria as the inoculum (62, 480). As a result, a variety of DTP vaccines were produced in the United States, which varied in their methods of production and generated different levels of antibody response (480, 481). Previous observational studies and clinical trials showed 70% to 90% efficacy of DTP vaccines to prevent serious pertussis disease (158, 482–484). To enhance the immunogenicity of the vaccine and reduce its adverse effects, vaccine was adsorbed onto an aluminum salt (284).

In 1970s, confidence in DTP vaccines began to decline in several countries after reports of local and systemic reactions surfaced in several locations (Table 6). In addition to reports of local skin reactions at the injection site, other less common but more serious systemic adverse events were linked to DTP, including neurological diseases such as encephalopathy, infantile spasms, and sudden infant death syndrome (485–487). Moreover, growing medical and public anxiety coupled with a heightened molecular structural knowledge of *B. pertussis* led to production of less reactogenic acellular pertussis vaccines (284). In Japan, Sato et al. designed the first purified-component DTaP vaccine (488). The initial acellular vaccines (Takeda-type vaccines) consisted predominantly of FHA, small amounts of inactivated PT, and, in some cases, fimbrial proteins and PRN. These constructs were followed by development of other acellular (Biken-type) vaccines containing equal amounts of PT and FHA. Newer DTaP vaccines contained purified immunogenic antigens and excluded LPS, which was present in the DTP vaccines (473, 489–493). In addition, the new-generation DTaP vaccines underwent rigorous testing for potential toxicity and potency in mice, while testing for potential adverse events and antibody response was done in children. The results of safety testing were reassuring and revealed that the efficacy of DTaP vaccines exceeded that of whole-cell DTP vaccines. Larger effectiveness trials and pertussis surveillance studies followed and proved that DTaP vaccines were effective and safe (284).

TABLE 6 Safety concerns identified from clinical trials and postlicensure studies of DTP, DTaP, and Tdap vaccines[a]

Vaccine (references)	Adverse events	Precautions	Contraindications
DTP (485–487, 664)	Mild Fever, fatigue, headache, dizziness, irritability, anorexia, local skin reaction at the injection site	Hypotonic hyporesponsive episode occurred within 48 h after vaccination; history of fever ≥105°F (≥40.5°C) within 48 h of receiving the vaccine	Previous anaphylactic reaction to the vaccine or its components; encephalopathy occurred within 7 days after vaccination and no other cause was identified[b]
	Moderate to severe Arthus reaction, severe limb swelling, temp ≥ 105°F (≥40.5°C), febrile convulsions, inconsolable crying in infants/children for more than 3 h, hypotonic hyporesponsive episodes	History of arthus reactions after receiving a tetanus toxoid-containing vaccine; Guillain-Barré syndrome occurred <6 wk after receiving a tetanus toxoid-containing vaccine; persistent crying in infants/children for more than 3 h after receiving the vaccine; moderate to severe acute illness, with or without fever; seizure ≤3 days after receiving the vaccine	
DTaP (473, 491, 664–666)	Local skin reactions (pain, whole-limb swelling, redness, hotness), fever, irritability	Hypotonic hyporesponsive episode occurred within 48 h after vaccination; history of fever ≥105°F (≥40.5°C) within 48 h of receiving the vaccine; history of arthus reactions after receiving a tetanus toxoid-containing vaccine; Guillain-Barré syndrome occurred <6 wk after receiving a tetanus toxoid-containing vaccine; persistent crying in infants/children for more than 3 h after receiving the vaccine; moderate to severe acute illness, with or without fever; seizure ≤3 days after receiving the vaccine	Previous anaphylactic reaction to the vaccine or its components; encephalopathy occurred within 7 days after vaccination and no other cause was identified
Tdap (326, 665, 667–669)	Local skin reaction (pain, swelling, redness, hotness) at injection site; spontaneous abortion	Guillain-Barré syndrome <6 wk after receiving a tetanus toxoid-containing vaccine; history of arthus reactions after receiving a tetanus toxoid-containing vaccine; moderate to severe acute illness, with or without fever	

[a] DTP, diphtheria toxoid, tetanus toxoid, and whole-cell pertussis; DTaP, diphtheria and tetanus toxoids and acellular pertussis; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.
[b] Subsequent doses should not be given if this occurs after one of the previous doses.

In 1981, Japan introduced DTaP vaccines exclusively into the national immunization schedule. Since then, the reported number of pertussis cases in Japan has been low (494–496). These results from Japan encouraged other developed countries to evaluate Japanese DTaP vaccines and to develop DTaP vaccines with additional antigens. Approximately 24 acellular pertussis vaccines have been designed, many of which were evaluated in large clinical trials (Fig. 2; see Table S1 in the supplemental material). Although acellular pertussis vaccines are now used routinely in the immunization programs of many countries, optimizing the formulation of acellular vaccines has proven to be challenging, in part because no simple method (e.g., use of a correlate of protection) exists to evaluate the protective efficacy of newer pertussis vaccines (188). Therefore, acellular pertussis vaccines vary with respect to manufacturer, number of components, quantity of each component, and methods of purification and toxin inactivation as well as incorporation adjuvants and excipients (492).

Acellular pertussis vaccines have been studied extensively. In 1995, Edwards et al. conducted a large clinical trial to compare the safety and immunogenicity of 13 DTaP vaccines and two DTP vaccines (see Table S1 in the supplemental material) (492, 493). The results of this study showed that all 13 DTaP vaccines were as immunogenic as or more immunogenic than DTP vaccines and were associated with substantially fewer and less-severe adverse reactions than standard commercial DTP vaccines. Another clinical trial was conducted in 1996 by Gustafsson et al. to determine the efficacy and safety of two-component DTaP, five-component DTaP, and DTP vaccines among approximately 10,000 Swedish infants (404). The efficacy of the vaccines was determined to be approximately 60% for the two-component vaccine, 85% for the five-component vaccine, and 48% for the DTP vaccine. Rates of local skin reactions (redness of ≥2 cm, tenderness, and nodule of ≥2 cm) and systemic adverse events (fever of ≥38°C, crying longer than 1 h, weakness, cyanosis, and pallor) were significantly higher after any dose of DTP vaccine than after the three DTaP vaccines.

More recently, in 2012, Zhang et al. conducted a Cochrane review of several clinical trials that evaluated the safety and efficacy of one-, two-, and multicomponent DTaP vaccines in children (489). In this review, the efficacies of multicomponent DTaP vaccines in preventing severe (~85%) and mild (71% to 78%) per-

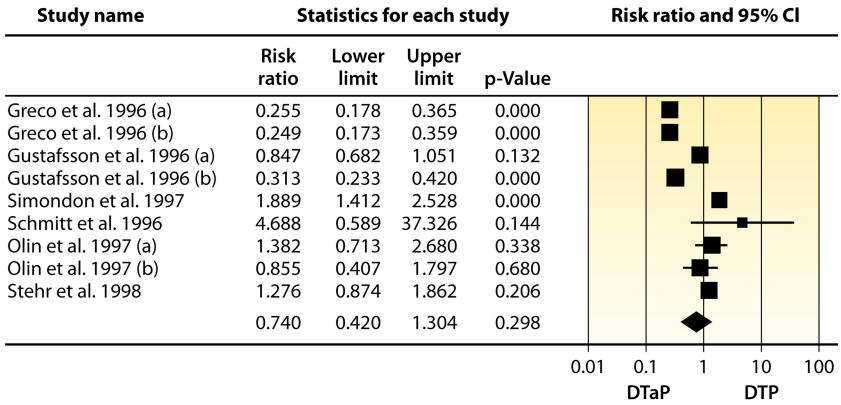

FIG 2 Forest plot of clinical trials reporting efficacy of acellular and whole-cell pertussis vaccines (38, 404, 590–593). See Table S1 in the supplemental material for additional details. Greco et al. (a) compared the efficacy of a three-component DTaP vaccine with that of DTP vaccine. Greco et al. (b) compared the efficacy of another three-component DTaP vaccine (from a different manufacturer) with that of DTP vaccine. Gustafsson et al. (a) compared the efficacy of a two-component DTaP vaccine with that of DTP vaccine. Gustafsson et al. (b) compared the efficacy of a five-component DTaP vaccine with that of DTP vaccine. Olin et al. (a) compared the efficacy of a three-component DTaP vaccine with that of DTP vaccine. Olin et al. (b) compared the efficacy of a five-component DTaP vaccine with that of DTP vaccine. DTaP, diphtheria and tetanus toxoids and acellular pertussis; DTP, diphtheria and tetanus toxoids and whole-cell pertussis.

tussis were similar. The estimated efficacies of one- and two-component DTaP vaccines were 59% to 75% to protect against severe pertussis but only 13% to 54% to protect against mild pertussis. In addition, the efficacies of DTP and DTaP have been shown to decrease over time after receipt of the fifth dose of either vaccine. In one study, the efficacy of DTaP vaccine declined from 98% to 71% (one year versus 6 years from fifth-dose completion) (497). In a large population-based study involved 15,286 participants, DTP vaccines yielded protection for 5 to 14 years (393). Although the efficacy of acellular pertussis vaccines in published studies varies by the number of *B. pertussis* antigens and manufacturer, a meta-analysis of several large pertussis vaccine trials showed no significant differences between DTaP and DTP vaccine efficacy against laboratory-confirmed pertussis (Fig. 2).

In the past 30 years, there has been a substantial increase in disease rates, and several pertussis outbreaks have occurred across the United States despite continued high DTaP vaccination uptake estimates among infants (174, 194, 201, 203–206, 271, 377, 476, 498). In addition, the epidemiology of pertussis has evolved such that pertussis in adolescents and adults continues to be a global concern even in countries with strong economies and high rates of childhood immunization, such as Australia, Belgium, Canada, Finland, France, Germany, Italy, The Netherlands, Spain, Switzerland, the United Kingdom, and the United States (174–187, 302, 499). This change in the epidemiology of pertussis has been reflected in the cases reported to the U.S. CDC and the European Center for Disease Prevention and Control (EUVAC). According to the U.S. CDC 2014 Provisional Pertussis Surveillance Report, the incidence rates of pertussis for the years 2013 and 2014 were approximately 151, 40, 22, 30, 25, and 2 per 100,000 persons for the age groups less than 6 months, 6 to 11 months, 1 to 6 years, 7 to 10 years, 11 to 19 years, and ≥20 years, respectively (500). In the 2010 EUVAC pertussis surveillance report, the incidence rates of pertussis across Europe were 15, 4, 5, 13, 10, and 2 cases per 100,000 persons for the age groups less than 1 year, 1 to 4 years, 5 to 9 years, 10 to 14 years, 15 to 19 years, and ≥20 years of age, respectively (501).

Several factors have been attributed to the increase in incidence rates and the shift in the epidemiology of pertussis, including lower immunization rates among adolescents and adults, waning immunity after receipt of acellular pertussis vaccines, an increase in the awareness of pertussis by health care providers caring for adolescents and adults, improvements in diagnostics and surveillance methods, evolution of *B. pertussis*, and the spread of other *Bordetella* species (239–241, 246, 499, 502–513).

Some vaccine experts believe that the relatively short duration of immunity offered by acellular pertussis vaccines is the most important factor that explains the trends of outbreaks, particularly among children 7 to 10 years old (193, 496). For example, during the California outbreak, children primed with DTP vaccines had longer-lasting immunity than those primed with DTaP (502). In Australia, a sustained pertussis epidemic occurred in the past several years, which is thought to be a result of the switch from DTP to DTaP vaccines (514). Other vaccine-preventable disease scientists do not believe that the change in the underlying *B. pertussis* epidemiology is sufficient to explain the pertussis upsurge in adults but instead believe that increased public awareness and the addition of PCR and single-point serological diagnosis are the major factors for the high rates of cohort cases reported (163, 193, 287). In addition, *B. parapertussis* is often underdiagnosed and cannot be ignored as a potential cause for pertussis outbreaks, because no vaccine is currently available to protect humans from this species (27).

The prevention of pertussis centers on the provision of pertussis vaccines in routine childhood immunization programs. These programs vary across countries where licensed pertussis vaccines have been administered to infants, children, and adults. In the United States, and based on the guidelines of the Advisory Committee on Immunization Practices (ACIP), the childhood immunization schedule for DTaP vaccine consists of five doses for children less than 7 years of age. These five doses are given at 2, 4, 6, and 15 to 18 months of age, and one booster dose is given at 4 to 6 years of age (515, 516). Although DTaP vaccines became widely used in many countries, including the United States, Canada, and Australia, in some Asian and many European countries, DTP vaccines are still the mainstay of pertussis prevention (182, 432, 517–519).

In the United States, despite great success of public health programs and availability of vaccines for disadvantaged children

TABLE 7 Recommended immunization schedule for DTaP and Tdap vaccines in the United States, 2008 to 2014[a]

Formulation (reference[s])	Dosage	Age or other group indication	Special recommendations
DTaP (515, 516)	Five doses for children <7 yr	2, 4, 6, and 15–18 mo and 4–6 yr	ACIP recommendation
Tdap (515)	Single dose	11–18 yr	Preferred age 11–12 yr; regardless of the timing from the most recent DTaP dose
Tdap (670)	Single dose	19–64 yr	In place of Td booster; in persons who have not previously received Tdap vaccine
Tdap (670)	Single dose	≥65 yr	In place of Td booster; in persons who have not previously received Tdap vaccine
Tdap (545, 671)	Single dose during each pregnancy	Pregnancy	Preferred at 27–36 wk of gestation; if the vaccine is not administered during pregnancy, it should be given immediately postpartum

[a] ACIP, Advisory Committee on Immunization Practices; DTaP, diphtheria and tetanus toxoids and acellular pertussis; Td, tetanus and diphtheria toxoids; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

through the federally funded Vaccines for Children Program, many children in medically underserved areas as well as in minority groups remain partially immunized or nonimmunized (520). Recent (2015) data from Detroit, MI, show that only 40% of children have completed the primary vaccination series and suggest that rates of underimmunization may exceed 50% in some populations (Michigan Care Improvement Registry, unpublished data). Such underimmunization suggests the need for improved local-, state-, and national-level immunization strategies to reach the Healthy People 2020 goals of 95% vaccine coverage for several pediatric vaccines (521).

Tdap Immunization for Adolescents and Adults

Even in countries with substantial childhood vaccination coverage (sometimes defined as ≥70%), the protection provided by vaccination tends to decrease over time due to waning immunity (155, 384). In 2003, Crowcroft et al. estimated that the proportion of susceptible children who became infected with *B. pertussis* was ~10 percent at 1 year after complete vaccination, 60% by 5 years, and 100% by 15 years (155). It has also been estimated that 80% of the current cases of pertussis occur because of waning immunity in household members who had been immunized against pertussis (522). Such data underscore the importance of booster vaccination among older children, adolescents, and adults. Recent immunization efforts have focused on adults, because the disease in this age group is often overlooked and unrecognized (225, 251, 282, 523). Moreover, adolescents and adults are usually the primary source of *B. pertussis* transmission to neonates and infants, who are at risk of infection themselves (476, 498, 524–527). As a result, another acellular pertussis vaccine (Tdap) was developed for adolescent and adult use.

Similar to DTaP vaccines, Tdap vaccines have demonstrated high levels of safety and immunogenicity. In a small group of adolescents ($n = 123$) aged 11 to 18 years who had never received *B. pertussis* antigen-containing vaccines and had no history of *B. pertussis* infection, 89% of participants mounted anti-PT antibodies, and all participants had an immune response to at least one *B. pertussis* antigens (FHA or pertactin) 29 to 49 days after vaccination (528). In 2007, Wei et al. investigated a pertussis outbreak at a private school on the island of St. Croix, U.S. Virgin Islands ($n =$ 499 students, nursery school through twelfth grade) to determine Tdap vaccine effectiveness (529). They determined that the estimated Tdap vaccine effectiveness was approximately 66%. In a large randomized clinical trial involving 802 participants aged 18 to 55 years who had completed childhood vaccination with DTP and were given monocomponent Tdap in that study, the antibodies to PT were mounted in 92% at 1 month after vaccine administration (530). In 2004, Purdy et al. conducted a cost-benefit analysis to determine whether Tdap administration in adolescents and adults would be a good strategy (531). They found that vaccination is most cost-effective among adolescents because they have the highest incidence of pertussis and pertussis-related complications in which disease-related costs were indirect (i.e., lost productivity at work and disrupted social activities). The results of that study revealed that booster immunization for adolescents 10 to 19 years of age would prevent 0.7 to 1.8 million pertussis cases and save 0.6 to 1.6 billion dollars over 10 years. After an extensive review of its cost-effectiveness, Tdap is now recommended by the ACIP for a wide range of the general population. Table 7 presents the ACIP recommendations for the Tdap vaccine.

A few years following release of the ACIP recommendations for Tdap vaccine, Koepke et al. conducted a population-based study to evaluate the effectiveness of Tdap vaccines in adolescents (532). Koepke and colleagues used the Wisconsin Immunization Registry to collect Tdap vaccination histories and reports of laboratory-confirmed pertussis among adolescents during the Wisconsin pertussis outbreak of 2012. The results of their study showed that the effectiveness of Tdap vaccines decreased over a short time regardless of vaccine manufacturer. The estimated effectiveness was ~75%, 68%, and 35%, and 12% for adolescents who received vaccines during 2012, 2011, 2010, and 2008/2009, respectively, with point estimates differing between the two Tdap vaccine brands. However, in 2015, Decker et al. critiqued the study conducted by Koepke et al., claiming that it was neither randomized nor conducted prospectively (533). In addition, Decker et al. claimed that the authors of that study were unable to control for brand-specific vaccine analyses, which could have been a potent confounding factor (533). While future studies are needed to evaluate the long-term effectiveness of available Tdap vaccines and until a more durable vaccine is produced, clinician scientists have recently suggested that Tdap vaccination should be started at the age of 9 years instead of that currently recommended (11 years of age) (534). They also suggested that a booster of Tdap vaccine should be administered every 5 to 10 years to every person. In addition, a booster of Tdap vaccine every 2 to 3 years during local

pertussis epidemics may also be considered. Other experts urge the production of a single-component monovalent acellular pertussis vaccine (i.e., free of diphtheria and tetanus toxoids), which could allow more frequent boosters in adults (535).

In the United States, most Tdap vaccines are administered in outpatient (ambulatory) clinic settings, community pharmacies, or public health departments (536, 537). Although Tdap vaccines are widely available in those settings, overall rates of Tdap immunization are still relatively low, particularly among adults (508). The U.S. CDC showed that the uptake of Tdap vaccine among adults was ~14% in 2014, while much higher vaccine uptake was reported among adolescents (i.e., ~80% in 2012), likely because it is required for school enrollment in many states (507, 508).

Tdap Immunization for Pregnant Women

During the last decade, 83% of whooping cough deaths occurred in infants under 3 months of age (538). Experts now recognize that household members were the primary source of pertussis infection for children (247, 249, 251, 524, 539–541). Although the source of infection (SOI) has not been identified in more than 50% of infant cases, mothers were recognized as the main SOI for an estimated 35% of infections in the United States (247, 250, 540). Additional information has emerged in a number of reports from Australia and The Netherlands indicating that older children have become the most common SOI to their infant brothers and sisters (253, 524, 542). In September 2015, Skoff and colleagues used enhanced pertussis surveillance data collected over an 8-year period (2006 to 2013) from seven states (Colorado, Connecticut, Massachusetts, Minnesota, Mexico, New York, and Oregon) to identify the most common source of pertussis infection in the United States (543). The results of this study showed that siblings (mean age, ~8 years) are the main SOI (35.5%), followed by mothers (20.6%), and fathers (10%).

As a result of ongoing community pertussis transmission to babies who are too young for pertussis vaccination, the ACIP released an updated set of recommendations to protect babies from pertussis. The ACIP concluded that administration of Tdap vaccine during pregnancy is safe and immunogenic (544–547). The ACIP recommended that pregnant women, preferably in the third or late second trimester, and all individuals who come into close contact with babies should receive one dose of Tdap vaccine (544). Nevertheless, as antibody titers decay after 1 year post-Tdap vaccination in healthy adults, maternal antipertussis antibodies also wane rapidly so that there is little persistent antibody in the mother at the time of the next baby, even if the mother is immunized during a prior pregnancy (548–551). Therefore, in 2012, the ACIP revised the recommendations and advised Tdap vaccine for all pregnant women and for each pregnancy irrespective of the interval between pregnancies (545). Studies have shown that efficient antibody transfer occurred from vaccinated mothers to babies via the placenta, although antibody levels are neither optimum nor long-lasting (545, 552, 553).

In October 2012, the United Kingdom introduced Tdap immunization for pregnant women. Since then, several studies have been conducted to evaluate vaccine safety and effectiveness. Based on preliminary data from the United Kingdom and Australia, babies born to vaccinated mothers are at lower risk of acquiring pertussis infection early in their lives than their unvaccinated counterparts (554). In 2014, Donegan et al. used the United Kingdom Clinical Practice Research Datalink to conduct a cohort study to examine the safety of pertussis vaccine in pregnancy (555). More than 20,000 pregnant women who received the pertussis vaccine and a matched unvaccinated control group were observed for development of vaccine-related adverse events. The results of this study showed no evidence of a higher risk of stillbirth in the 2 weeks after vaccination or later in pregnancy. In addition, compared with the cohort of unvaccinated women, there was no evidence of a higher risk of premature delivery, stillbirth, maternal or neonatal death, pre-eclampsia, eclampsia, hemorrhage, fetal distress, low birth weight, or any other serious pregnancy- or delivery-related complications. Another study by Amirthalingam et al. analyzed 82 lab-confirmed infant pertussis cases identified from 2008 to 2013 in the United Kingdom Clinical Practice Research Datalink to assess maternal Tdap vaccine effectiveness (556). Vaccine effectiveness in infants born after 1 October 2012 and younger than 3 months at onset was 91% (95% confidence interval [CI], 84% to 95%). In 2015, Dabrera et al. conducted a case-control study in England and Wales for the period from October 2012 through July 2013 to determine the effectiveness of maternal Tdap vaccine in protecting infants from pertussis (557). PCR or culture was used to confirm pertussis in clinically suspected disease in infants aged less than 8 weeks. Mothers of 10 cases and 29 controls received Tdap in pregnancy. The results in this study showed an adjusted Tdap vaccine effectiveness of 93% (95% CI, 81% to 97%).

Since the ACIP recommendations for pregnant women were issued, several concerns have been raised. In 2014, Jiménez-Truquehas and Edwards (558) summarized those concerns as follows: (i) the safety profile of Tdap vaccine for both mothers and babies has not been extensively evaluated, (ii) the high concentration of antibodies transmitted transplacentally could minimize an infant's immune response to pertussis-containing vaccine (559), and (iii) serological interference between maternal antibodies and infant antibodies after pertussis-containing vaccine can occur (553). More recent comments about the ACIP recommendations were provided by Boyce and Virk (534), who expressed concern that passive antipertussis immunity will not allow for sufficient herd immunity to protect infants from community exposures. Moreover, they asserted that the duration of protection yielded by maternal antibodies transfer is relatively short-lasting and will not impact the substantial morbidity that pertussis causes outside the period of infancy.

To address some of these concerns, Hardy-Fairbanks et al. conducted a cohort study in which 70 pregnant women were enrolled to evaluate the effect of maternal Tdap vaccination on infant immunological responses to routine pediatric vaccines (553). At delivery, pertussis antibody titers among women receiving Tdap vaccine during pregnancy ($n = 16$) were approximately 2- to 20-fold higher than those in the control group (unvaccinated women, $n = 54$). Umbilical cord antibody titers were approximately 3- to 36-fold higher in vaccinated women than in unvaccinated women. They also found that infants whose mothers were vaccinated with Tdap during pregnancy maintained adequate antibody concentrations even after the first dose of DTaP vaccine was administered. However, slight declines in the immune response following the primary series of DTaP vaccine were observed in the Tdap group compared with controls, but no differences in immune response remained following the booster dose.

Additional studies suggest that there is no evidence of the interference between Tdap vaccine-induced maternal antibody and

DTaP immunization among infants reported in previous studies of acellular pertussis vaccines (560, 561). In 2014, Munoz et al. conducted a double-blind randomized controlled trial to evaluate the safety and immunogenicity of Tdap vaccine ($n = 33$) or placebo ($n = 15$) given during the third trimester of pregnancy, with crossover vaccination postpartum (561). At delivery, antibody titers in women who received Tdap vaccine during pregnancy were higher than those in women who received vaccine after delivery ($P < 0.001$). Also, infants of mothers vaccinated with Tdap vaccine during pregnancy had higher immune responses at birth ($P < 0.001$) and at age 2 months ($P < 0.001$) than those of women who received a placebo in the third trimester. Antibody responses in infants born to mothers vaccinated with Tdap in pregnancy were not different following the fourth dose of DTaP vaccine from those in infants whose mothers were not vaccinated during pregnancy. This trial found no Tdap-associated serious reactions among infants or mothers. Developmental milestones and growth were similar in both infant groups.

In contrast, in 2014, Kharbanda et al. (562, 563) conducted a retrospective cohort study to determine the risk of chorioamnionitis, preterm birth, pregnancy-induced hypertension, and small size for gestational age in 220 women with singleton pregnancies who received Tdap vaccine during the index pregnancy. They found that 6.1% of women exposed to the Tdap vaccine were diagnosed with chorioamnionitis, compared with 5.5% of those who did not receive the vaccine (adjusted relative risk [RR] = 1.19; 95% CI, 1.13 to 1.26). No other statistically significant results were noted. Pertussis experts have encouraged more epidemiological studies and clinical trials to assess the duration of protection that antepartum immunization would offer to infants in order to better understand the immune response to pertussis vaccines and to implement more efficient strategies that would overcome existing barriers to vaccinating pregnant women (410, 564–566). In the efforts to interrupt the circulation of *B. pertussis*, several options have been suggested, including vaccination of all pregnant women, vaccination of all of an infant's close contacts, lowering the start date of infant immunization, reinstituting use of DTP vaccines, and adding another *B. pertussis* antigen (e.g., AC or BrKA antigen) to existing DTaP vaccines (193, 287). In 2008, Halasa et al. conducted a randomized controlled trial among 50 neonates aged 2 to 14 days (567). Two subgroups of these neonates received DTaP vaccine either alone or in combination with hepatitis B vaccine. They found that the additional dose of DTaP at birth was safe but was significantly associated with lower responses to several pertussis antigens than in controls.

Despite national recommendations for maternal Tdap vaccination, the Tdap vaccine has been provided to only a fraction of eligible women in the United States. In 2013, data from California Department of Public Health indicated that only 25% of hospital-delivering women received Tdap vaccine during pregnancy (554). Another national report found that fewer than three percent of pregnant women received maternal Tdap vaccination (568). In Michigan, the average uptake of Tdap vaccine among pregnant women who are enrolled in the Medicaid health insurance plan was approximately 14% (569). In a recent commentary, pediatric specialists at the University of California Los Angeles Medical Center (UCLA) observed that most mothers were not vaccinated with Tdap during pregnancy (566). Since that report, the UCLA health system has mandated that obstetrics and gynecology clinics maintain a stock of Tdap vaccine for perinatal vaccination of expectant and new mothers.

Types of Vaccines

Currently, both whole-cell and acellular pertussis vaccines are distributed by manufacturers in Belgium, Bulgaria, France, India, Indonesia, Italy, and South Korea. Whole-cell vaccines are available in combination with conjugate *Haemophilus influenzae* type b vaccine, enhanced inactivated poliovirus vaccine, or hepatitis B virus vaccine (284). Since 1996, in the United States, only acellular pertussis-containing vaccines are shown in the recommended immunization schedule. There are five U.S. Food and Drug Administration-licensed DTaP vaccines for infants and young children, and they vary in the amount and number of antigens in the vaccine. In addition to diphtheria and tetanus toxoids, the vaccines also contain other pertussis components as follows. Certiva (Baxter Laboratories) is a monocomponent vaccine that contains only PT antigen. Tripedia (Sanofi Pasteur) is a dual-component vaccine containing PT and FHA, while Infanrix (GlaxoSmithKline) is a triple-component vaccine containing PT, FHA, and PRN. In the United States, the combination of Infanrix, hepatitis B vaccine, and inactivated poliovirus vaccine is marketed as Pediarix (GlaxoSmithKline). Pediarix is supplied in single-dose, thimerosal-free vials or prefilled syringes and is licensed for a three-dose primary series in infants born to mothers without hepatitis B surface antigen. Acel-Immune (no longer manufactured) and Daptacel (Sanofi Pasteur) are four-component vaccines that contain PT, FHA, PRN, and FIM2 (Acel-Immune) or PT, FHA, PRN, and FIM2,3 (Daptacel) (163, 284).

Tdap vaccines (under the brand names Adacel and Boostrix) are licensed in the United States for immunization of adolescents and adults. Adacel (Sanofi Pasteur) is a five-component acellular pertussis vaccine. Adacel is licensed for use in the United States in persons 11 to 64 years old and is supplied in thimerosal-free, single-dose vials. Boostrix (GlaxoSmithKline) is a three-component acellular pertussis vaccine. In the United States, Boostrix is licensed for use in persons 10 years of age and older (284).

FUTURE RESEARCH AVENUES

If Jules Bordet were alive today, he surely would take some pride in the millions of lives saved in the past several decades through the use of pertussis vaccines. At the same time, he might also argue that additional work remains to be done to eliminate the disease he once observed in his own children (571). The resurgence of pertussis and changes in strain characteristics suggest that some *B. pertussis* strains may now evade the immune response elicited by existing vaccines. Fortunately, new tools from multiple disciplines are now available to us provide a rich arsenal to guard against the risk of global complacency in the control of pertussis. Research leads from microbiology, public health, and vaccinology highlight at least six avenues of research in pertussis (Table 8). While animal models for pertussis have been instrumental in increasing our understanding of pertussis pathogenesis, multidisciplinary collaborations will be essential to identify host-pathogen and other factors that drive evolution of *B. pertussis* strains circulating in populations around the world (572–574). Such studies may identify environmental, ecological, and human-related factors (e.g., biofilms, use of antibiotics, vaccines, immunity, or behaviors) that are associated with *B. pertussis* disease and strain emergence (133, 135). Vaccines with improved adverse event profiles and that provide higher efficacy will provide protection to vulnerable populations, including neonates, very young infants, and older adults (575). In these populations, research to understand *B. pertussis* virulence factors associated with vaccine-associated ad-

TABLE 8 Future directions in pertussis research

Research avenue	Potential opportunities	Challenges
Environmental, ecological, epidemiological, and host-pathogen factors that drive evolution of *B. pertussis* strains	Studies in populations of young children, adolescents, and adults to complement research using animal models of infection with *B. pertussis*	Requires ongoing access to populations such as those in infant and child care centers; requires multidisciplinary collaboration with clinicians, emergency departments, and hospitals, including those in resource-limited settings
Design and manufacturing of pertussis vaccines that possess more favorable adverse event profiles and/or are safe for neonates compared with currently licensed pertussis vaccines	Studies examining diverse immunological signatures among immunized neonates, infants, and children with different pertussis vaccine formulations; investigation of safe new adjuvants will complement work (see below) in identifying new vaccine antigens	Lack of business case for private sector investment requires cogent business case for public-private partnership models such as those stimulated by the Gates Foundation
Novel designs for higher-efficacy pertussis vaccines that work in infants, adolescents, and adults	Studies using reverse genetics as applied for other new vaccine development may facilitate and hasten identification of novel antigens; elucidation of cell-mediated immunity (Th-1, Th-17) and mucosal (IgA) immunity	Understanding of pertussis genetics and immunological protection in different age groups and bodily compartments is needed to identify key antigens for inclusion in new-generation vaccines; using immunosignature data, need to establish new correlates of protection and indicators of long-term protection
Intelligent surveillance systems that quickly identify laboratory-confirmed pertussis cases and formulate real-time strategies for outbreak control	Development and testing of machine learning algorithms that allow rapid processing of large amounts of data into actionable information at local levels (e.g., city, county, state/province)	Requires access to large electronic surveillance databases or modeled data to test algorithms; requires implementation science expertise to evaluate optimal surveillance processes
Population studies to understand changes in pertussis epidemiology that may result from changes in mucosal environment, biofilms, and bacterial colonization	Studies to understand changes in mucosa-*B. pertussis* interaction among infants, children, and adults vaccinated with conjugate vaccines that affect bacterial colonization	Other pathogen and environmental exposures introduce substantial heterogeneity of interactions across different populations
Development and evaluation of dynamic models that identify conditions under which local or regional pertussis reemergence might be predicted and the potential role of booster doses in different countries to prevent pertussis reemergence	Development of country and regional models based on improved, laboratory-based pertussis surveillance data and use of different vaccine formulations and schedules	Integration of microbial evolutionary genetic changes based on empirical analysis of strains globally is needed to optimize model outputs

verse events may take advantage of immunosignature analysis (576). Immunosignatures in different age groups will also aid the understanding of factors driving humoral and cell-mediated immunity among infants, children, and adults with naturally acquired pertussis and following pertussis vaccination (577). Identification of novel adjuvants to use with existing or new pertussis vaccines has the potential to augment immune responses, including cell-mediated immunity, across a wide range of ages (578). Comparative studies using microbiome analysis among vaccinees and pertussis cases as well as studies to examine the role of probiotic supplementation with vaccination may yield new strategies for prevention or mitigation of disease severity (579). In the fields of public health and clinical medicine, electronic health information systems are prevalent in areas where pertussis outbreaks have been reported (580). Existing information technology and new telecommunication systems may be leveraged to integrate case finding and communication among health care providers and public health agencies with diagnostic testing and guidance for prophylaxis and treatment that facilitates early termination of pertussis outbreaks (581). Such new-generation disease surveillance systems may be adaptable to mobile platforms, particularly in low- and middle-income countries with limited hardwire broadband capacity, and may benefit control of pertussis and many other diseases (582–586). Strengthened surveillance for pertussis cases among vaccinees and nonvaccinees will help shed light on the emergence and distribution of vaccine-induced escape strains of *B. pertussis* that may emerge in different parts of the world (510, 511). A global network, perhaps coordinated through WHO, would collect strains and provide access to strains for collaborating laboratories to perform genome sequencing that characterizes gene mutations. Decreasing costs of whole-genome sequencing now make this genetic analysis feasible. Because vaccine-induced escape strains may be relatively rare, alerting national reference laboratories to collect and store such strains will accelerate genomic analysis.

Further research is also needed to understand changes in pertussis epidemiology that may result from changes in the mucosal environment, biofilms, and bacterial colonization in the nasopharynx and other mucosal sites induced by other vaccines. Studies to understand the role of maternal immunization and its influence on the immunological response to other vaccines in neonates and older infants will help guide improved vaccine design and vaccine schedules. In the area of maternal immunization, additional clinical, epidemiological, and pathological studies are needed to understand the role and significant of conditions (e.g., chorioamnionitis) observed in association with use of Tdap vaccination. In addition, research to better understand the role of the innate immune system, including potential for pertussis adaptation, may also shed light on avenues for combating the ability of *B.*

pertussis to inhibit complement activation mediated by molecules such as the Vag8 autotransporter (587, 588).

Finally, further development and evaluation of dynamic models will help identify conditions under which a pertussis reemergence might be predicted and will aid in evaluating the potential role of booster doses, novel vaccines for neonates and other ages, and newly adjuvanted vaccines to prevent pertussis reemergence (589). New models will benefit from access to empirical data on the genetic characteristics of emerging pertussis strains that evade current vaccines or the human immune response to natural infection.

CONCLUSIONS

B. pertussis remains a pathogen of global importance despite having been a recognized cause of whooping cough for one hundred years. Although high vaccination coverage among infants has been achieved in many countries, pertussis cases and deaths are reported annually among children and adults. In existing surveillance systems, underreporting, particularly among adolescents and adults, remains an ongoing multifactorial challenge due to factors including low awareness of pertussis among health care professionals, lack of standardized and efficient diagnostic assays, and weak surveillance infrastructure in many countries. At present, neither currently available vaccines nor previous *B. pertussis* infection can provide long-lasting protection against later infection. Multipronged approaches to develop new vaccines or enhance the currently available vaccines (e.g., development of more durable and less reactogenic vaccines) will likely require global initiatives aimed at creating new-generation pertussis vaccines through public-private partnerships. The rapid improvement of laboratory research methods in the fields of genomics, immunology, and bioinformatics heralds a new era in research on pertussis that will allow for integration of disciplines and sharing of global research tools such as *B. pertussis* isolates. The next decade promises new opportunities to understand the evolution of pertussis virulence of strains around the world. This knowledge combined with a deepened understanding of humoral, innate, and cell-mediated immunity to pertussis has potential for guiding new opportunities for treatment and prevention of pertussis across the life span.

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