Fall November, 2015

Pertussis Review Publication 2015.pdf

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Protecting Newborns Against Pertussis: Treatment and Prevention Strategies

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Abstract Pertussis is a potentially severe respiratory disease, which affects all age groups from young infants to older adults and is responsible for an estimated 195,000 deaths occurred globally in 2008. Active research is ongoing to better understand the pathogenesis, immunology, and diagnosis of pertussis. For diagnosis, molecular assays (e.g., polymerase chain reaction) for detection of Bordetella pertussis have become more widely available and support improved outbreak detection. In children, pertussis vaccines have been incorporated into routine immunization schedules and deployed for pertussis outbreak control. Lower levels of vaccine coverage are now being observed in communities where vaccine hesitancy is rising. Additionally, recognition that newborn babies are at risk of pertussis in the USA and UK has led to recommendations to immunize pregnant women. Among adolescents and older adults in the USA, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular pertussis (Tdap) Vaccines are recommended, but substantial individual- and system-level barriers exist that will make achieving national Healthy People 2020 targets for immunization challenging. Current antimicrobial regimens for pertussis are focused on reducing the severity of disease, reducing rates of sequelae, and minimizing transmission of infection to susceptible individuals. Continued surveillance for pertussis will be important to identify opportunities for reducing young infants’ exposure and reducing the impact of outbreaks among school-aged children. Laboratory-based surveillance for newly emerging strains of B. pertussis will be important to identify strains that may evade protection elicited by currently available vaccines. Efforts to develop new-generation pertussis vaccines should be considered now in anticipation of vaccine development programs, which may require ten or more years to deliver a licensed vaccine.

Key Points

- Pertussis should be considered a serious and potentially deadly infectious disease in infants.
- Although vaccines for pertussis are widely available for all ages, low vaccine uptake among pregnant women and other adults is a continued problem.
- Given currently available vaccines, future research to enhance vaccine effectiveness and the duration of protection should be encouraged.
- Recent increases in pertussis outbreaks suggest the need for increased vaccine advocacy and education, particularly in affected communities that may be at continued risk.
1 Introduction and Clinical Presentation

Pertussis—also known as “whooping cough”—is caused by the Gram-negative coccobacilli bacteria Bordetella pertussis [1]. Pertussis has ancient roots from the sixth century, when it was described as the “cough of 100 days” in China [2]. In the early nineteenth century, Jules Bordet and Octave Gengou isolated B. pertussis from a sputum sample from Bordet’s son when he had a cough illness [3]. In its clinical course, the classical progression of pertussis can be divided into three consecutive stages (the illness [3]. In the clinical course, the classical progression of pertussis can be divided into three consecutive stages (the catarrhal, paroxysmal, and convalescent stages). Each stage may last for up to 3 weeks, and, typically, full recovery from the illness occurs in 2–3 months [4–7]. In the catarrhal stage, the pertussis diagnosis is often missed because of the presence of signs and symptoms that overlap with viral upper respiratory tract infections. Healthcare professionals, including pediatricians and primary care providers, need to maintain a high index of suspicion for pertussis when they encounter patients in whom a persistent cough is the presenting complaint [5]. In the paroxysmal stage, patients usually experience intense cough episodes, which may last for several minutes. Cough paroxysms are usually associated with inspiratory whoops, bluish discoloration of mucous membranes, eye bulging, tongue protrusion, excessive salivation, and watery eyes. Soon after each cough episode, patient may also experience vomiting, fatigue, and respiratory exhaustion [8]. In the convalescence stage, the cough pattern decreases in its intensity and duration, but a milder form of cough may remain for up to 6 weeks. However, in recovering children, cough paroxysms similar to pertussis may recur if a child becomes sick with a respiratory viral infection [5, 6, 9, 10].

For families, health systems, and society, the impact of pertussis is immediate, substantial, and attended by long-term consequences. Health outcomes associated with pertussis range from mild clinical illness (which may be treated in outpatient settings) to severe disease (requiring intensive care unit support), as well as complications that result in death. In older children, adolescents, and adults, signs and symptoms of pertussis may be overlooked [11–14]. In neonates and young infants, who may be too young to complete the primary series of pertussis vaccine, such missed diagnoses may have devastating clinical consequences [15]. In infants and newborns who develop complications of pertussis, the most common findings that are observed include apnea, high rates of hospitalization, pneumonia, weight loss, otitis media, convulsions, and death [16]. The aim of this review is to provide up-to-date information about the disease epidemiology, available diagnostic tools, prevention, post-exposure prophylaxis (PEP), and treatment of pertussis.

2 Epidemiology and Disease Burden of Pertussis

2.1 Global Burden of Pertussis

Pertussis is a disease with a global distribution and remains one of the leading causes of vaccine-preventable deaths [17]. On the basis of 2008 disease burden estimates (the most recent year for which data are available) from the World Health Organization (WHO), pertussis is responsible for ~16 million cases and 195,000 deaths worldwide. Approximately 43% of reported pertussis deaths have occurred in Africa [18]. The lack of national data on pertussis from laboratory-based surveillance systems in many countries has led to challenges in maintaining current global disease burden estimates.

2.2 Pertussis Burden in the USA

Over the past two decades in the USA, pertussis has been the most commonly reported vaccine-preventable disease associated with severe morbidity and mortality among infants [19–24]. For the last several years, the nationwide incidence of pertussis has dramatically increased in a wide range of ages, with neonates and young infants experiencing the highest rates of illness and sequelae (Fig. 1). In 2012, the incidence of pertussis was approximately 127/100,000 for infants <1 year of age, with a 15% case-fatality rate reported among infants <3 months of age [25]. In 2013, the rates of pertussis were approximately 160 and 45 per 100,000 for infants aged <6 months and those aged 6–11 months, respectively, with 12 deaths reported among infants <3 months of age [26]. In 2014, the incidence of pertussis among infants <6 months of age was approximately 151/100,000 infants, and for those aged 6–11 months, the incidence rate was 40/100,000 infants. In 2014, a total of seven deaths were reported among infants <3 months of age [27]. The rates of infant hospitalizations associated with pertussis far exceed those observed in older age groups. For instance, previous reports showed that ~50% of infants with pertussis require hospitalization, whereas the hospitalization rate among adolescents and adults was ~6% [16, 28, 29]. A large proportion of hospitalized infants require intensive care and respiratory support [16].

Like other countries, the USA has experienced a number of pertussis outbreaks over the last two decades. The pertussis resurgence has been linked to many factors. One of these factors is the high vaccination exemption rates across the country, where many states offer nonmedical waivers for school requirements. These include exemptions for religious and parent personal beliefs [30–32]. In the last 5 years, at least five large pertussis outbreaks have been
reported from geographically diverse areas, including California, Michigan, Minnesota, Ohio, and Washington. In 2012, Washington State experienced a large outbreak, in which most county jurisdictions were affected, and officials reported a total of 4918 confirmed and probable cases, for an overall incidence of ~11/100,000 [33, 34]. In this outbreak, the incidence among infants was 107/100,000. Among a total of 95 confirmed infant pertussis cases, 35 infants required hospitalization [33]. During the California pertussis outbreak of 2014, state officials reported a record number of cases (n = 10,831) [35]. Among the reported cases, 376 required hospitalization and 227 cases (60 %) were identified among infants <4 months of age. Eighty-five infants (23 %) required intensive care. Four infants <2 months of age died.

On the basis of routinely reported pertussis surveillance data from state health departments, several areas in the USA reported unusually high numbers of pertussis cases to the US Centers for Disease Control and Prevention (CDC) during the period from 2009 to 2014. In total, health departments reported 26,566 pertussis cases from California [35], 3038 from Michigan [36], 4144 from Minnesota [37], 2958 from Ohio [38], and 6231 Washington [33].

2.3 Pertussis Burden in Europe

In the European Union (EU) and associated countries, pertussis data from 2012 have shown an overall incidence rate of ~11/100,000, and the number of pertussis cases has more than doubled in comparison with previous years (2008–2011) (Table 1; Fig. 2). In 2012, 38,840 cases were reported by 28 EU/European Economic Area (EEA) countries and, of these countries, 26 have national surveillance systems that capture pertussis reports. Although comparison between countries should be done only with caution because of variations between surveillance systems and different degrees of awareness in the reporting of the disease, the highest incidence rates of pertussis were reported from Norway (85.2/100,000), the Netherlands (76.9/100,000), Denmark (20.4/100,000), the UK (19/100,000), and Slovakia (17/100,000) [15].

In the same European Center for Disease Prevention and Control (ECDC) report of 2012 pertussis data, confirmed cases of pertussis were reported most frequently among young children and adolescents aged 5–14 years, in whom a relatively higher incidence rate of 23.7/100,000 was noted. The higher incidence of pertussis in this age group has been attributed to the fact that Norway and the Netherlands had the highest overall notification rates, with particularly high rates among children aged 5–14 years. However, in several other European countries, children aged <5 years experienced the highest incidence rates of pertussis (23.6/100,000 population). Overall, females had a slightly higher incidence rate of pertussis, with a female to male case ratio of 1:0.86.
2.4 Pertussis Burden in Other Countries

In other regions of the world, pertussis continues to threaten infants and children. From 2011 through 2013, a large pertussis outbreak struck Auckland, New Zealand, and led to 62 confirmed pediatric intensive care unit (PICU) pertussis hospitalizations among children aged 2 weeks through 3 years, and 98% of the children admitted to the PICU were <6 months of age [39]. In these New Zealand children with severe pertussis, the mean length of stay was 12 days, resulting in 783 patient-days for these hospitalized children. In that hospital, a total of six deaths were reported from 2003 to 2013, with three occurring from 2011 to 2013. The total cost of the 2011–2013 pertussis outbreak was ~NZ$3 million, and the estimated annual cost of pertussis management in the PICU was ~NZ$82,000.

In many countries, such as South Korea and Italy, there is significant underreporting of pertussis in established disease surveillance systems [40–42]. Previous studies have suggested that passive surveillance may result in an underestimation of the actual pertussis incidence by a factor of 10–1000 [43, 44]. In 2015, national surveillance reports from the China Center for Disease Control showed total figures of 1712 pertussis cases in 2013 and 3408 pertussis cases in 2014 from a total country of 1.364 billion residents, suggesting the presence of gross underreporting in China [45, 46]. A recent study in China implemented active surveillance to determine the incidence rates of pertussis over 2 years (2010–2012) in three communities

Table 1 Laboratory-confirmed pertussis cases reported in the European Union/European Economic Area (EU/EEA), 2008–2012

<table>
<thead>
<tr>
<th>Country</th>
<th>2012 Cases</th>
<th>Ratea</th>
<th>2011 Cases</th>
<th>Rate</th>
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a Rates are expressed as cases per 100,000 population

△ Adis
with a total population of ~160,000 [41]. In this study, Huang and colleagues screened >1000 individuals with a clinical picture suggestive of pertussis. A total of 1022 nasopharyngeal (NP) swabs were tested by polymerase chain reaction (PCR), and 802 blood samples were tested for antibodies to *B. pertussis* toxin (PT). Of those tested, pertussis was confirmed in 113 individuals, showing an annual incidence of pertussis of 23.5/100,000 in this population. These results showed an incidence rate from active surveillance that was 16 times higher than the incidence observed during passive surveillance over the same time period. For individuals aged 15–69 years, the actual incidence rate of pertussis was ~43 times higher than reported hospital rates. Notably, 85% of pertussis cases among children <15 years of age were reported among children who had been previously immunized with a primary series of pertussis-containing vaccine. Huang and others showed that only 5% of pertussis cases were accurately diagnosed at their first clinic visit. This study in China underscores the challenge found in many countries, where pertussis may be underdiagnosed when cases initially present to clinical facilities [47, 48].

Several factors explaining the resurgence of pertussis have been suggested [49–56]. These include waning immunity following natural infection or vaccination; improved surveillance methods; improved availability of diagnostic tests (e.g., PCR), leading to increased case detection; increased awareness of pertussis among healthcare providers, leading to increased case reporting; incomplete pertussis immunization series, leading to breakthrough disease; and changes of antigenic structure and adaptation of *B. pertussis*, which may escape antibodies elicited by currently available vaccines. In 2010, King et al. conducted an analytic study using microarray-based comparative genomic hybridization to determine the gene content of *B. pertussis* strains in 171 *B. pertussis* isolates from Australia, Japan, Kenya, the Netherlands, Senegal, and Sweden, with different vaccination schedules between 1949 and 2008 [57]. The results of this study showed that *B. pertussis* is dynamic and is continuously evolving as a result of adaptive evolution.

### 3 Cost of Pertussis Illness

Starting in 2001, work by the Global Pertussis Initiative suggested that the direct and indirect costs associated with pertussis are substantial [58]. Direct costs associated with pertussis include charges associated with doctor visits, urgent care or emergency room visits, inpatient hospitalization, diagnostic laboratory tests, and radiologic tests, as well as therapeutic intervention costs. Indirect costs include school and work absences, reduced work productivity, and time away from work for parents who care for a sick child. The direct costs tend to be higher in infants than in other age groups because of higher rates of pertussis complications, which often require hospitalization or intensive care.

In 2000, Lee and colleagues estimated the economic burden of pertussis for 87 individuals among diverse age groups in 69 households [59]. This group found that the direct costs associated with pertussis averaged $2800 for infants, $300 for children, $250 for adolescents, and $180 for adults. In this study, indirect costs amounted to an average of $767 per family and an average of six lost work days. In a separate study from 2004, the average total cost of pertussis among adults was higher than that for children ($1950 versus $800) [60]. The direct costs associated with pertussis treatment were higher for adults ($330) than for children ($240), and the indirect costs associated with pertussis were 90% higher for adults than for adolescents ($450 versus $155). In 2014, Lopez et al. found that
pertussis-associated hospitalizations in young infants (aged 0–6 months) increased 53% from $14,520 in 1997 to $22,278 in 2009 [61]. If severe neurologic sequelae of pertussis, such as encephalitis, are taken into account, the direct medical costs of pertussis may be much higher. In two Canadian studies, the direct medical costs for children with pertussis-associated encephalitis or chronic neurologic deficits were approximately $27,640 and $103,650 Canadian dollars, respectively [62, 63].

In 2014, McGarry et al. conducted a cost-effectiveness study to evaluate Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis (Tdap) vaccine introduction for individuals aged 65 years and older [64]. In their modeling, McGarry et al. showed that the costs of treating mild, moderate, and severe pertussis were ~$83–102, $203–607, and $6432–13,029, respectively. In this study, the cost of illness in infants (aged <1 year) with moderate to severe pertussis was almost double the cost in other age groups.

4 Laboratory Diagnosis

Early detection and diagnosis of pertussis relies on a high index of suspicion, collection of appropriate clinical laboratory specimens, and rapid application of available diagnostic tests for pertussis (Table 2). Delays in diagnosis and treatment of pertussis facilitate its transmission to household contacts, friends, schoolmates, and family members [65–67]. Although typical pertussis may be diagnosed on clinical grounds alone, the assessment of clinical manifestations may be unreliable particularly in patients who manifest atypical presentations that mimic other infections [68]. Culture-based diagnosis of *B. pertussis* is considered definitive and is assumed to have absolute specificity in association with an unexplained cough. In the past two decades, advances in laboratory diagnosis of pertussis have enabled earlier disease detection. For example, culture and direct fluorescent antibody staining of NP secretions have been largely replaced by nucleic acid amplification tests—notably, PCR [69].

PCR is a nucleic acid amplification test, which detects DNA sequences of *B. pertussis* in clinical respiratory specimens. PCR is becoming widely used in many clinical settings and provides a timely diagnostic tool that does not require viable organisms and can be used up to 4 weeks after the onset of a cough [70–73]. After the fourth week from cough onset, *B. pertussis* DNA diminishes in the nasopharynx, resulting in low PCR sensitivity and thus high false negative results [72]. Although the sensitivity of PCR is estimated to be 19% higher than that of culture alone, PCR gives lower specificity and more frequent false positive results than culture [12, 70, 71, 74, 75]. False positive results can be due to several factors—most notably, contamination of specimens during sample collection with either the native organism or an ampiclon created from a previous reaction [76]. Ideally, specimens should be collected and vaccines administered in separate areas, using a careful technique and decontamination of surfaces. It is also paramount to test only patients who are symptomatic [73]. To avoid errors in PCR detection of pertussis, the test should be used only in patients whose clinical presentation is suggestive of pertussis and before initiation of antibiotic treatment [72, 75]. In addition, when PCR is used to test asymptomatic close contacts for pertussis, the test result should not drive any clinical decision related to PEP [72].

In the last two decades, several enhancements of PCR assays have improved test specificity and performance. The test has changed substantially from agarose gel or microwell plate detection of amplicons to real-time amplification and detection [69]. Most PCR tests for pertussis are based on detection of an insertion sequence (IS)—a transposable DNA element approximately 1000 base pairs (bp) long, which has been inserted into multiple sites on the same chromosome. There are usually multiple copies of an IS per genome, which increases the sensitivity of PCR tests. IS481 is perhaps the most well described and validated target for *B. pertussis* [69], and for detecting *Bordetella parapertussis*, IS1001 is most commonly used [77–79]. There are >50 copies of IS481 per *B. pertussis* genome [80]. However, IS481 is also present in other *Bordetella* species, such as *Bordetella holmesii* and *Bordetella bronchiseptica* [80, 81].

To enhance the specificity of the test, PCR tests that target more than one IS have recently been developed and evaluated [71, 82]. In 2007, Qin et al. compared the use of a three-IS-targeted real-time PCR assay (IS481, PT ptxA

<table>
<thead>
<tr>
<th>Table 2 Diagnostic tests for <em>Bordetella pertussis</em></th>
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<tr>
<td><strong>Test</strong></td>
</tr>
<tr>
<td><strong>Bacterial culture</strong> [72, 79, 198–200]</td>
</tr>
<tr>
<td><strong>PCR</strong> [79, 197, 199, 201, 202]</td>
</tr>
<tr>
<td><strong>Serology</strong> [72, 94, 198, 200, 202–205]</td>
</tr>
<tr>
<td><strong>DFA</strong> [72, 197, 198]</td>
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</tbody>
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*DFA* direct fluorescent antibody, *NP* nasopharyngeal, *PCR* polymerase chain reaction
promoter region, and outer membrane porin, or recA) versus a conventional single-target sequence (IS481) in respiratory specimens collected from >4000 patients with suspected pertussis [71]. In comparison with the single-target IS, the three-target combination increased the proportion of truly positively identified specimens by 1.25-fold, and two-target combinations increased the proportion of positively identified specimens by 1.10- to 1.24-fold. In 2013, Tizolova et al. screened the genomes of recently circulating isolates of Bordetella species by using PCR to compare the prevalence rates of IS481, IS1001, and IS1002 with previously published data, and to sequence all IS that were detected [83]. Tizolova and colleagues confirmed that targeting IS481 and IS1001 did not provide high test specificity, because multiple species were detected, including B. pertussis, B. holmesii, B. bronchiseptica (IS481), B. parapertussis, and B. bronchiseptica (IS1001).

Another PCR-based diagnostic tool, the FilmArray Respiratory Panel (RP), has also been developed and evaluated [84]. Although RP kits are appropriate for a core laboratory or point-of-care clinic because of their ease of use, they have less sensitivity than real-time PCR [84]. Jerris et al. recently compared the FilmArray RP and a focused B. pertussis PCR assay in 71 clinical specimens [84]. The RP targets the promoter region of the PT gene, whereas the focused real-time PCR assay targets IS481. They concluded that the FilmArray RP assay detects approximately one third fewer cases of B. pertussis than the focused PCR assay.

Although PCR is the nucleic acid amplification test most frequently used to detect B. pertussis, an assay based on loop-mediated isothermal amplification (LAMP) has also been developed [85–87]. LAMP is a relatively new, rapid method to amplify DNA, with high sensitivity and specificity, and has been developed and commercialized to target a number of pathogens, including B. pertussis. The method consists simply of incubating a mixture of the target gene, 4–6 different primers, Bst DNA polymerase, and substrates. The advantages of the LAMP method are that it has high amplification efficiency without the need for thermal cycling and therefore is less costly [85, 87–89].

The results from PCR testing should be considered in the context of clinical symptoms of pertussis to guide therapeutic decision-making [73]. To optimize diagnose and case detection, clinicians and public health staff should utilize standardized NP swab specimen collection methods, as described by the CDC [90]. Either an NP swab or NP aspirates are considered adequate for culture or PCR testing [90].

Serologic testing has high sensitivity for pertussis diagnosis, particularly at a late stage in the illness when the bacteria are no longer detectable [91]. Although serology is not a useful diagnostic tool in neonates or young infants [73], antibody titers could be of value for diagnosis in adolescents and adults, who usually seek medical advice late in the disease course when culture and PCR would be less reliable [92]. In addition, two serum specimens collected several weeks apart to demonstrate a fourfold or greater change in the immunoglobulin (Ig) G titer are required [69]. The WHO includes paired serology as part of the criteria for laboratory confirmation of pertussis.

Although serologic testing is done in many countries and is within the laboratory confirmation criteria of the WHO [93], standardized assays are not widely available in the USA and are less often used [73]. In Massachusetts, the state health department offers a positive single-point PT-specific IgG serology to support improved surveillance and confirmation of pertussis in individuals aged 11 years and older [28, 75, 94]. In states other than Massachusetts, cases meeting the clinical case definition that are seropositive but culture- or PCR-negative should be reported as probable cases [72].

The most meaningful serologic results are obtained using enzyme-linked immunosorbent assay (ELISA)-based formats with purified antigens, such as PT and filamentous hemagglutinin (FHA). Because PT is produced only by B. pertussis, detection of PT antibodies constitutes the most specific serologic indicator of pertussis infection [95–99]. Unfortunately, serologic diagnosis is complicated by the fact that PT is present in substantial amounts in all acellular vaccines. Therefore, antibodies generated by infection versus vaccination cannot be definitively distinguished for at least 6 months after vaccination [100]. Because of the continuous circulation of B. pertussis in the population, anti-PT IgG is likely detectable in most adolescent and adult populations, so it is necessary to establish a cutoff value correlated with recent infection. Thus, accurate interpretation of serologic results requires knowledge of both the vaccination history and possible exposures to determine the reason for detectable antibody responses to B. pertussis [73].

5 Post-Exposure Prophylaxis and Treatment

Supportive care is the mainstay of management for B. pertussis and may include hospital admission for close monitoring of respiratory status and fluid or nutritional support. Furthermore, known triggers for coughing paroxysms (e.g., cold temperatures) should be avoided [101, 102]. In addition to supportive management, antimicrobial agents are recommended for prophylaxis of family members and other close contacts to help reduce the risk of secondary cases regardless of vaccination status [103]. The decision to prescribe antibiotics for close contacts should be made on a case-by-case basis. Factors that could
influence this decision include the exposure duration and intensity, high-risk group membership (e.g., infants <1 year old), and the potential for developing a severe form of pertussis [6]. Macrolide antibiotics are recommended as chemoprophylaxis agents. For infants aged >1 month, children, and adults, erythromycin or clarithromycin are preferred agents. In neonates, azithromycin is the PEP drug of choice [104, 105].

Macrolide antibiotics are also considered first-line agents for the treatment of pertussis (Table 3) [105]. These antimicrobials are most effective when given early in the course of the disease—ideally, in the catarrhal stage [105, 106]. In addition to decreasing the severity of the disease, antimicrobial treatments are effective in clearing the nasopharynx of B. pertussis in symptomatic and asymptomatic individuals and consequently preventing the spread of the infection [107–109]. Erythromycin has been the antibiotic of choice for treatment of pertussis or PEP, but, because of potentially uncomfortable side effects (e.g., gastrointestinal upset), which result in poor adherence to the treatment regimen, the newer macrolides (i.e., clarithromycin and azithromycin) have been prescribed more often [105]. In 1999, Halperin et al. conducted a double-blind controlled trial to determine whether erythromycin for PEP is effective in household contacts [110]. Halperin and colleagues studied 152 culture-confirmed cases of pertussis in children, and the household contacts of those confirmed cases were randomly assigned to receive either erythromycin (40 mg/kg/day in three divided doses) or placebo for 10 days. It was found that erythromycin successfully eradicated B. pertussis in ∼68 % of household contacts. In 2007, Altunaiji et al. conducted a Cochrane review of 13 clinical trials involving >2000 participants to assess the risks and benefits of antimicrobial treatment of, and PEP against, whooping cough in children and adults [107]. They found that short-term antibiotics (azithromycin for 3–5 days; clarithromycin or erythromycin for 7 days) were as effective as long-term erythromycin (for 10–14 days) to eradicate B. pertussis from the nasopharynx. Erythromycin and clarithromycin are contraindicated for use in neonates (i.e., <1 month old). Evidence-based medical reports have linked the use of erythromycin to the development of infantile hypertrophic pyloric stenosis (IHPS) in neonates [105, 111]. Azithromycin is recommended by the American Academy of Pediatrics as the antibiotic of choice for neonates (<1 month old) [105]. However, recent research has suggested a strong association between azithromycin exposure and the risk of IHPS in the first 2 weeks of life, with an adjusted odds ratio of 8.26 (95 % confidence interval 2.62–26.0) [112].

Trimethoprim–sulfamethoxazole (TMP–SMX) is used as an alternative to macrolides but should be limited to use in children aged >1 month and in adults when macrolides are not well tolerated [105]. In addition, because of the potential risk of kernicterus in newborns, pregnant women and nursing mothers should avoid ingestions of TMP–SMX [105].

In severe pertussis, exchange transfusion therapy has demonstrated effectiveness when administered early in the disease course. The goal of exchange transfusion is reduction of hyperleukocytosis, which may be as high as 100,000/mm³ [113–121].

### 6 Pertussis Immunization

Routine childhood immunization is the most effective strategy to prevent transmission and disease associated with pertussis and other vaccine-preventable diseases. Pertussis-containing vaccine schedules, including the primary immunization series, vary considerably from country to country. Although diphtheria–tetanus–acellular pertussis (DTaP) vaccines have become widely used by many developing and developed countries [122–124], a few countries (e.g., India and Poland) offer whole-cell pertussis-containing (DTwP) vaccine in their national childhood immunization schedules [124, 125]. India administers DTwP to children aged 6, 10, and 14 weeks, 16–24 months, and 5 years. In contrast, Germany immunizes children by using DTaP at ages 2, 3, 4, and 11 months [124], while countries such as Italy, Finland, Norway, and Sweden offer DTaP vaccines at 3, 5, and 11–13 months of age. Immunization schedules for pertussis vaccines used in infants and children across the EU can be

<table>
<thead>
<tr>
<th>Agent</th>
<th>Age group (months)</th>
<th>Dosing information</th>
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<tbody>
<tr>
<td>Erythromycin [105, 107, 108, 206, 207]</td>
<td>&gt;1</td>
<td>40–60 mg/kg/day in 3 or 4 divided doses for 7–14 days</td>
</tr>
<tr>
<td>Azithromycin [105, 107–109, 207]</td>
<td>&lt;6</td>
<td>10 mg/kg daily for 5 days</td>
</tr>
<tr>
<td>Clarithromycin [105, 107, 109, 207]</td>
<td>≥6</td>
<td>10 mg/kg on day 1, followed by 5 mg/kg on days 2–5</td>
</tr>
<tr>
<td>TMP-SMX [105]</td>
<td>&gt;2</td>
<td>15 mg/kg/day in 2 divided doses for 7 days</td>
</tr>
<tr>
<td>SMX sulfamethoxazole, TMP trimethoprim</td>
<td></td>
<td>TMP 8 mg/kg/day plus SMZ 40 mg/kg/day every 12 h for 14 days</td>
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</tbody>
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Table 3 Antibiotics for pertussis treatment and post-exposure prophylaxis in infants and children

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found online at https://euvac.net and through the ECDC [126]. In the USA, the primary vaccination series for DTaP vaccine includes four doses at the ages of 2, 4, 6, and 15–18 months, with a fifth booster dose at the age of 4–6 years [123, 127].

It is well known that immunity to pertussis is not long-lasting. The results of several epidemiologic studies have estimated that protection following natural infection may last for up to 30 years [128–131]. Other studies have found that protection gained from administration of whole-cell pertussis vaccines may last for up to 14 years [132–138]. However, the immunity following immunization with acellular pertussis vaccines ranges from 4 to 7 years [135, 139–143]. The available data suggest that licensed acellular pertussis vaccines may be associated with faster waning of immunity, which may enable increased pertussis transmission among adults, children, and neonates, in comparison with the available whole-cell vaccines [144].

In the last 10 years, >80 % of pertussis-associated deaths have occurred among neonates and infants under 3 months of age [145]. In response to this observed disease burden, selected countries (i.e., the USA and the UK) have recommended maternal Tdap vaccination [146, 147]. The goal of maternal immunization is to protect young infants, particularly those <3 months of age, through transplacental passive transfer of IgG antibodies to newborns. Maternal pertussis immunization during the third trimester of pregnancy appears to offer optimal antibody transfer to newborns. In general, pertussis-containing vaccines are considered safe for the mother and the infant, as well as resulting in relatively high B. pertussis IgG antibody concentrations [146, 148–150]. However, studies have shown that antibody transfer conferred neither optimal nor long-lasting protection [148, 151–153].

In 2011, the CDC Advisory Committee on Immunization Practice (ACIP) recommended routine Tdap vaccination of all pregnant women after 20 weeks’ gestation. During the ACIP’s deliberations, it was noted that antibody titers decline within 1 year post-Tdap vaccination in healthy adults, including women in the postpartum period [154–157]. For this reason, the ACIP has now recommended that women receive one dose of Tdap in the third trimester of each pregnancy [146, 148]. For women who have missed Tdap vaccination during pregnancy, they may still receive a dose immediately postpartum, with benefit to the mother as well as her newborn baby. Although the rate of Tdap vaccine uptake among mothers increases in the postpartum period, the impact of postpartum Tdap immunization on newborns is less than that of Tdap vaccine administered during pregnancy [158]. In 2012, Castagnini et al. conducted a cross-sectional study to compare the effectiveness of postpartum Tdap immunization among a predominantly Hispanic urban population in Texas before and after release of the 2008 CDC recommendation for postpartum Tdap vaccination. No differences in pertussis hospitalizations, hospital lengths of stay or deaths associated with infant pertussis were observed from the pre- to the post-recommendation eras. The adjusted p value, odds ratio, and 95 % confidence interval were 0.87, 1.06, and 0.5–2.2, respectively [159].

Although Tdap vaccination is strongly recommended for pregnant women in the USA, national reports indicate that Tdap vaccine uptake during pregnancy is low. The California Department of Public Health estimated that only 25 % of pregnant women received the vaccine in 2013 [160]. Other nationwide estimates of Tdap vaccine uptake showed that <3 % of pregnant women are immunized against pertussis during pregnancy [161].

In many countries—including the USA, France, and Australia—a “cocooning” strategy has been implemented to protect young infants who are too young to be immunized or who may be partially immunized [162]. This strategy involves immunization of all household contacts (with DTwP/DTaP or Tdap as appropriate for age), including parents and other family members immediately after childbirth [153, 163]. However, complete immunization of household members and other contacts whom the newborn may encounter poses substantial programmatic challenges to ensure widespread vaccine availability, as well as provider education and outreach to ensure timely Tdap immunization of fathers and postpartum women and routine DTaP immunization of age-eligible children [164, 165]. Encouragingly, recent data reported in 2014 from the UK suggested that maternal Tdap immunization is 91 % effective in preventing pertussis among newborns <8 weeks of age [166].

Many industrialized countries—including the USA, Canada, France, Germany, and Australia—have introduced Tdap vaccine into their adult immunization programs to reduce pertussis-associated morbidity and mortality in young infants [124]. The ACIP recommends a single-dose routine Tdap immunization of adolescents at 11–18 years of age (preferably at ages 11–12 years) regardless of timing from the most recent DTaP dose. For adult age groups, the ACIP recommends a single dose of Tdap in place of tetanus–diphtheria (Td) vaccine for persons aged 19–64 years, and for those aged 65 years and older who have not received Tdap vaccine previously, a single dose of Tdap vaccine is also recommended [167]. Although Tdap vaccines are widely available, the overall uptake of Tdap vaccine among adults remains relatively low (~ 14 %). In contrast, among adolescents aged 13–17 years, the CDC showed that the uptake of Tdap vaccine was ~80 % in 2012.

Many studies have supported vaccination of healthcare workers (HCWs) because they place patients at increased
risk of acquisition of *B. pertussis*, particularly unimmunized individuals, partially immunized infants, and immunocompromised individuals [67, 168–173]. Despite recommendations for HCWs Tdap immunization, vaccine acceptability among HCWs and Tdap immunization rates are not optimal. In 2012, Walther and colleagues implemented an HCWs immunization program for a Swiss medical institution soon after national adoption of an HCWs Tdap immunization recommendation [174]. Between 2012 and 2013, of 852 eligible HCWs, 427 (51 %) responded to the call. Seventy-two (17 %) had already been vaccinated with Tdap within the previous 10 years, 304 (71 %) received Tdap, and 12 (3 %) declined Tdap immunization. The research team concluded that comprehensive efforts are necessary to mobilize reluctant HCWs and to achieve higher Tdap vaccine uptake.

7 New Pertussis Vaccine Antigens and Adjuvants

The current limitations of existing whole-cell and acellular pertussis-containing vaccines (e.g., the limited duration of protection) have inspired discussion around strategies for improving the available vaccines. Improved pertussis vaccines would induce high levels of protective antibodies, long-term protection, equivalent or higher vaccine efficacy, and lower rates of adverse events following immunization. To date, acellular pertussis-containing vaccines have contained a maximum of five *B. pertussis* antigens, including PT, FHA, pertactin (Prn), fimbriae serotype 2 (fim 2) and fimbriae serotype 3 (fim 3). A previously studied antigen, adenylate cyclase (AC), is not included in the currently available acellular pertussis vaccines [175–177]. New research is underway to study the safety and immunogenicity of this potential new addition to the pertussis vaccine antigenic armamentarium.

Other antigens offer potential for improving existing pertussis vaccines. Iron regulatory proteins 1–3 (IRP 1–3) have shown promising results as potential vaccine antigens in animal models [178]. To date, no research has been undertaken to study the addition of IRP 1–3 to currently available acellular pertussis vaccines and potential improvements in vaccine safety and immunogenicity in humans. In addition, an autotransporter (BrkA) was tested in preclinical studies but was found not to induce a significant immune response when added to DTaP and DTwP vaccines in a mouse model [179]. It is important to note that the genetic sequence of BrkA is conserved across all *B. pertussis* isolates tested, including isolates that are Prn deficient and PT deficient. These observations suggest that BrkA may have a capacity for inducing more broadly protective immunity [180].

Pertussis vaccine adjuvants have also been an area of research interest. Current vaccines employ alum (in the form of aluminum gel or aluminum salts) as an adjuvant, which is believed to provide greater stimulation of the T helper (Th)-2 immune response versus the Th-1 response. However, current evidence suggests that a strong Th-1 immune response is required for clearance of *B. pertussis* [181, 182]. For this reason, new adjuvants, such as those containing CpG oligodeoxynucleotides, have been developed and tested in animal models. CpG motifs are believed to induce significant Th-1 and Th-17 immune responses and yield longer-lasting immunity [183–186]. Additional work to identify new safe and effective antigens and adjuvants for pertussis vaccines represents an important line of research over the next decade.

8 Live-Attenuated Pertussis Vaccines

In 1980, Roberts and colleagues reported the results of work with a *B. pertussis* aroA mutant strain, which appeared to induce high-level antibodies against *B. pertussis* in mice immunized by aerosol with the *B. pertussis* aroA mutant strain [187]. Such vaccine constructs may have utility when applied in a prime-boost immunization strategy in which the aroA mutant strain is administered as the priming vaccine dose. In addition, a live-attenuated BPZE1 pertussis vaccine has been developed that induces both humoral and cell-mediated immunity [182, 188–190]. Additional animal studies have shown that BPZE1 is safe and may protect airways from allergen-driven interleukin (IL)-4, IL-5, and IL-13 [191, 192]. A BPZE1 vaccine has been studied in a phase I, randomized, double-blind clinical trial and was shown to be safe and to induce transient colonization when administered to healthy adults [193]. Additional clinical trials of the BPZE1 pertussis vaccine will open soon for recruitment in Sweden (ClinicalTrials.gov study ID: NCT02453048).

9 Future Development of New-Generation Pertussis Vaccines

At present, whole-cell and acellular pertussis vaccines are used throughout a range of developed and developing countries. Active development of new-generation pertussis vaccines would benefit all countries but would have particular benefit in saving lives among infants and children living in developing countries. In the older model of vaccine introduction, developed country manufacturers traditionally introduced new vaccines into wealthier nations, and these new vaccines then become available in developing countries several years or decades later. In the past
10 years, innovative models of financing for development and introduction of vaccines, such as the Advanced Market Commitment (AMC) have used pneumococcal conjugate vaccine (PCV) and public–private partnerships (e.g., the Meningitis Vaccine Project), which bring together foundations, manufacturers, research organizations, lending organizations, and government agencies, often under the auspices of the Global Alliance for Vaccines and Immunizations (GAVI) [194]. Accelerating development of needed new-generation pertussis vaccines will require active engagement among leading global health organizations, such as the WHO and the CDC, as well as foundations such as the Bill and Melinda Gates Foundation [195].

10 Conclusions

Despite increases in the vaccination coverage achieved for pertussis-containing vaccines in many developed and developing countries, pertussis control remains elusive, with frequent pertussis outbreaks worldwide. These concerning events highlight the need for more effective surveillance and immunization strategies, as well as new-generation vaccines against pertussis. Future strategies to augment pertussis control efforts should include (1) improved surveillance to monitor for pertussis outbreaks, as well as the emergence of new Bordetella pertussis strains (Prn-deficient strains); (2) more widespread and timely access to pertussis diagnostic tests; (3) immunization programmatic evaluations that improve provider education and accessibility of existing Tdap vaccines for adolescents, pregnant women, and other adults; and (4) rigorous evaluation of carefully implemented cocooning strategies.

Since the development of acellular pertussis vaccines in 1980s, little work has been dedicated to the development of new pertussis vaccines that provide high-level and durable protection against pertussis. Although new B. pertussis antigens, adjuvants, and vaccination routes have been explored in animal models, relatively few new pertussis vaccines have entered human clinical trials. Notably, a promising live-attenuated pertussis vaccine is currently in phase I clinical trials. If this experimental vaccine succeeds through all phases of the clinical trials, it may represent an important addition to the childhood immunization schedule and offer an additional tool for control of adolescent and adult pertussis [196]. Finally, enhancing vaccine uptake among pregnant women, adolescents, and adults, including HCWs, may be essential to reducing the burden of pertussis across a range of developed and developing countries globally.

Acknowledgments All authors—Abdulbaset Salim, Yan Liang, and Paul Kilgore—played a key role in the development of this manuscript.

Compliance with Ethical Standards

Funding No funding was received for this work.

Conflict of interest Abdulbaset Salim, Yan Liang, and Paul Kilgore declare that there are no conflicts of interest to report.

References


Pertussis Control Strategies


126. European Center for Disease Prevention and Control. Scientific panel on childhood immunisation schedule: diphtheria–teta


128. Wissing von Konig CH, Postels-Multani S, Bock HL, Schmitt HJ. Pertussis in adults: frequency of transmission after house-

129. Wendelboe AM, Van Rie A, Salmaso S, Englund JA. Duration of immunity against pertussis after natural infection or vacci


140. Guiso N, Begue P, Cohen R. Comparison of pertussis antibody levels in children up to 5 years of age primed at 2, 3, 4 months and boosted in a second year of life with either DTPA or DTPW based combination vaccines in France. Toronto; International Conference on Antimicrobial Agents and Chemotherapy; 2000.


146. Centers for Disease Control and Prevention. Updated recommenda-
tions for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months—Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morbid Mortal Wkly Rep. 2011;60(41):1424.


148. Centers for Disease Control and Prevention. Updated recommenda-


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