Bordetella pertussis – the cause of pertussis or whooping cough – is an exclusively human pathogen. Disease elimination by vaccination should, therefore, be possible, but has proved elusive. Many industrialised countries with long established immunisation programs are currently seeing a resurgence of pertussis, despite universal vaccination with high uptake, with the highest burden in the least immunised age groups (infants under 6 months of age and persons over 10 years old). However, low recognition and reporting and insensitive diagnostic tests mean that the true burden of pertussis is still underestimated. Recently, efforts to improve diagnostic yield include the expanded use of polymerase chain reaction and serological tests but both have significant limitations. The range of antibiotics available for treatment and prophylaxis has expanded to include the newer macrolides, azithromycin and clarithromycin, and a range of universal and targeted vaccination strategies have been implemented or proposed. This paper reviews the current epidemiology of pertussis in developed countries, including modes of clinical presentation, diagnosis, management and potential vaccination strategies.

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1940s there was a marked decline in reported pertussis disease. However, despite universal vaccination programs with high uptake, many industrialised countries, including the United States, France, Canada and Australia, have had a significant resurgence of notified pertussis in the past decade, particularly among adolescents and adults.2-3

In adults and older children, the diagnosis of pertussis is often delayed because of lack of classic symptoms and/or low physician awareness, resulting in the potential to transmit infection for several weeks.4 The true incidence of pertussis is poorly defined because of varying levels of clinician suspicion and reporting practices and limited diagnostic test sensitivity, even for newer tests, such as polymerase chain reaction (PCR). This is particularly true for older populations with less typical and often later clinical presentation. Currently, the true incidence of pertussis is generally considered to be substantially higher than reported by either notifications or hospitalisations in both developed and less developed countries.6,7 Culture of B. pertussis — still the gold standard for diagnostic specificity — has always been hampered by the fastidious nature of the organism and the limited period during which even meticulous practice can yield a positive culture, particularly in vaccinated persons. Recent efforts to improve the accuracy of diagnosis include increased use of PCR and single high titre pertussis serology. However, both have significant limitations. The often poor tolerance and therefore compliance with traditional macrolide therapy for treatment and prophylaxis of pertussis, as well as doubts about its efficacy, has led to clinical trials with the newer macrolides, clarithromycin and azithromycin.8,9

This review will examine:

- current epidemiology of pertussis and recent changes in the burden of disease
- clinical presentations in infants and adolescents
- diagnostic methods
- treatment and prophylaxis
- vaccination strategies for prevention.

EPIDEMIOLOGY OF PERTUSSIS

Surveillance of pertussis in most countries is based on clinical notifications and laboratory reports. In developed countries with long-established vaccine programs, the general trend has been for increasing incidence with a shift to infection in older persons, although the highest incidence continues to be in infants too young to be eligible for vaccination. Comparison of pertussis incidence between countries is problematic due to differences in case definitions, access to diagnostic tests, clinician awareness and reporting practices and whether pertussis is notifiable under public health legislation. Differences in immunisation strategies and historical levels of immunisation coverage within and between countries also affect the epidemiology of pertussis. Clinical recognition of disease due to B. pertussis infection is often poor, especially in adults and older children, who are more likely to present with atypical findings, on a background of waning immunity from infection or prior vaccination.

Developing countries

Recent reports of pertussis epidemiology from Asia, Africa and South America are limited but World Health Organization (WHO) estimates demonstrate that these countries have the highest disease burden.7,10 Estimating rates of pertussis is difficult, because of lack of access to diagnostic methods, misdiagnosis, under-reporting, and different reporting criteria between countries. For example, in Brazil, no increase in pertussis was documented following introduction of pertussis vaccination in the 1980s11 and in Argentina, few epidemiologic studies are available.12 Despite these constraints, it is clear that pertussis remains one of the top 10 causes of death in children under 1 year old worldwide with an estimated 10 million cases and as many as 400 000 pertussis-related deaths annually, 90% in developing countries and mostly in infants.2,13,14

Developed countries

A resurgence of pertussis has been well documented in many industrialised countries.14-17 In countries with well-developed immunisation programs, such as the United States, Australia and Canada, pertussis is now a problem in two broad age groups — those over the age of 10 years and those under the age of 5 months.3,15,16,18,19 The former group were often born in an era of low immunisation coverage, with waning immunity in those who were vaccinated while the latter cannot be fully protected by current vaccine schedules.

Pertussis in infancy

Rates of pertussis infection remain highest in infants, especially under the age of 6 months (Table 1). In New South Wales, Australia, a significant reduction in pertussis-related hospitalisations in the most highly vaccinated age group (5 months to 9 years) was documented but hospitalisations for pertussis under the age of 5 months remained unchanged.20 In the US, the mean annual incidence of pertussis in infants under 4 months of age increased from 63.4 cases per 100 000 in the 1980s to 88.7 cases per 100 000 in the 1990s.15 From 2001 to 2003, the highest annual incidence was in infants under 6 months of age (98.2 per 100 000), compared with 12.3 per 100 000 in infants aged 6–11 months.21 In European countries the highest incidence rates are also in infants but are not increasing.22-24 In Canada, 89% of infants admitted with pertussis to tertiary
hospitals between 1991 and 2001 were under the age of 6 months with most deaths under 3 months of age.18

Pertussis in older children and adolescents

In Europe, the surveillance project EUVAC-NET has recorded a 115% increase in incidence rates in children aged over 14 years between 1998 and 2002.23 Increased pertussis incidence in adolescents (aged 10–19 years) has also been documented in the US, from 5.5 per 100 000 in 2001 to 10.9 per 100 000 in 2003.21 Data from the Acellular Pertussis vaccine trial (APERT) conducted in the US suggest that the incidence of pertussis infection (defined serologically) in adolescents and adults is around 1% per year (range 0.4–2.7%)29 while the estimated annual incidence of symptomatic pertussis documented in 10–49 year olds by culture, PCR or serology in a prospective clinic-based study was 0.5% (507 per 100 000 person years).30

In Sweden, a different scenario pertains, with pertussis vaccination using acellular vaccines re-commenced in 1996, following a 17-year lapse caused by concerns over the efficacy and safety profile of the locally manufactured whole cell pertussis vaccines. Total rates of pertussis decreased by 80–90% from 89–150 per 100 000 in 1996 to 17–26 per 100 000 in 1996–2000.31 Similarly, there has been a reduction in hospitalisations due to pertussis in Sweden.32 However, the age-specific incidence in 8–14 year olds was similar in the pre-vaccine and the diphtheria-tetanus-acellular pertussis (DTPa) vaccine era, suggesting that B. pertussis has continued to circulate in school-age children despite infant pertussis vaccination.31

Population-based serosurveys using standardised antibody titres as a marker of infection have been used in Australia33 and several countries in Western Europe.34 Data from these surveys confirm a high prevalence of immunoglobulin (Ig)G to pertussis toxin (PT), consistent with pertussis infection in the previous 12 months, in a significant proportion of adolescents.

POSSIBLE EXPLANATIONS FOR CURRENT EPIDEMIOLOGY

The possible reasons for the change in epidemiology leading to increasing rates in those under 5 months old and those over 10 years in developed countries with well-established immunisation programs are numerous and include the following:

- duration of protection and waning immunity following infection and vaccination
- incomplete protection from vaccination
- infection source for infants
- infection source for adolescents
- strain polymorphism
- increased diagnosis and reporting.

Duration of protection and waning immunity following infection and vaccination

Waning immunity following infant vaccination and reduced opportunities for boosting immunity due to reduced circulation of pertussis may both contribute to increased susceptibility to pertussis infection and disease during adolescence.35–37 Estimates of the duration of protection following whole cell pertussis vaccination range from 4 to 14 years and following DTPa vaccination (based on limited studies) approximately 5–6 years.36 Age cohorts experiencing increased incidence of pertussis have been identified in Canada related to waning immunity from a less effective vaccine used with high coverage,4 and in Australia related to low vaccine uptake of a moderately effective whole cell vaccine.38

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Pertussis hospitalisation rates in infants &lt;1 year of age in several industrialised countries 86</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>Year</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------</td>
</tr>
<tr>
<td>USA</td>
<td>1990–1999</td>
</tr>
<tr>
<td></td>
<td>1997–2001</td>
</tr>
<tr>
<td></td>
<td>1995–1996</td>
</tr>
<tr>
<td>Canada</td>
<td>1989–2000</td>
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<td>1990–1998</td>
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<td>1998–2000</td>
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<td></td>
<td>2001–2002</td>
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<td></td>
<td>1995–1997</td>
</tr>
<tr>
<td>France</td>
<td>1993–1994</td>
</tr>
<tr>
<td></td>
<td>1996–2003</td>
</tr>
<tr>
<td>Austria</td>
<td>1990–1999</td>
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<td></td>
<td>1997–2001</td>
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<td></td>
<td>1995–1996</td>
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<td>Canada</td>
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<td>1998–2000</td>
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<td>1995–1997</td>
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<tr>
<td>France</td>
<td>1993–1994</td>
</tr>
<tr>
<td></td>
<td>1996–2003</td>
</tr>
</tbody>
</table>
Incomplete protection from vaccination

Two or more doses of a pertussis-containing vaccine appear to be needed for protection. Infants under 5 months old are too young, under most immunisation schedules, to have reliably received two or more doses. In Australia, half of all pertussis hospitalisations between 1994 and 2004 occurred in infants under 12 weeks of age, eligible to receive only one dose of pertussis-containing vaccine at 8 weeks of age. In a multinational study, approximately 75% of hospitalised infants had received no or one dose only of pertussis vaccine.

Infection source for infants

Adults, particularly parents, are the most important source of infection for infants. Individuals with pertussis disease are most infectious during the initial catarrhal period and for the first 2 weeks of spasmodic cough, but can remain infectious for up to 6 weeks, especially in the case of non-immune infants. A probable scenario is that adults and adolescents, who become infected because of waning vaccine or disease-induced immunity, act as reservoirs for infection and transmit infection to unvaccinated or partially vaccinated infants. In Australia, a national study identified a presumptive source of infection in 60% of 110 hospitalised infants, of whom 60% were parents. Parents were also identified as a common infection source in a French hospital-based study. In a household transmission study in Brazil, three-quarters of infants under 6 months of age were infected by people over 11 years old. In addition to parents, other adults in close contact with young infants such as grandparents and healthcare workers can be responsible for transmission.

Infection source for adolescents

School outbreaks have been documented in both the US and Australia as significant markers of transmission of pertussis among adolescents.

Strain polymorphism

It has been suggested that B. pertussis has adapted to express PT and pertactin (PRN) strains distinct from the vaccine strains, with consequent reduction in vaccine effectiveness, especially in the Netherlands and Finland. Recent studies in Finland have noted that B. pertussis has documented conformational changes in one region of PRN and suggested that reduced vaccine-induced immunity to this strain may account for increased pertussis infection. However, despite evidence of polymorphism for PT and PRN in several countries, no direct link to vaccination programs or their efficacy has been proved.

Increased diagnosis and reporting

In developed countries it is likely that improved diagnostic techniques and reporting has made a major contribution to increased notification rates for pertussis. A recent study in Toronto, Canada, reports that a marked increase in pertussis incidence in 2006 was associated with a markedly increased volume of tests performed, primarily PCR-based assays. Increased press reports and scientific literature on the ‘resurgence of pertussis’, as well as reports of pertussis vaccine trials and subsequent licensure of low dose acellular pertussis vaccines for use in adults, may have also led to an increase in clinician awareness and reporting. In many developing and some developed countries, identification of pertussis is still limited by patient and physician awareness and the limited sensitivity of diagnostic tests. In infants, increased rates of pertussis may be related to both changes in vaccination strategies and infection sources as well as the availability of PCR as a diagnostic tool.

DIAGNOSIS

The identification and clinical management of pertussis requires a combination of clinical suspicion, appropriate laboratory tests and consideration of antibacterial therapy (see algorithm in Table 2).

Clinical diagnosis

Suspicion of pertussis may be prompted by clinical signs and symptoms or by a history of exposure to a confirmed case. Clinical diagnosis is problematic because of the wide spectrum of disease manifestations (both in those with partial immunity due to past vaccination and in unimmunised infants) and awareness of clinicians. The sensitivity and specificity of laboratory tests is influenced by the use of antibiotics early in the course of infection, mixed infections, recent immunisation and time since symptom onset, as well as inherent limitations in insensitivity.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical management algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical suspicion of pertussis</strong></td>
<td></td>
</tr>
<tr>
<td>- Coughing illness more than 2 weeks (or cough of any duration with contact with a confirmed case)</td>
<td></td>
</tr>
<tr>
<td>- Paroxysms</td>
<td></td>
</tr>
<tr>
<td>- Inspiratory whoop</td>
<td></td>
</tr>
<tr>
<td>- Post-tussive vomiting</td>
<td></td>
</tr>
<tr>
<td><strong>Epidemiological links</strong></td>
<td></td>
</tr>
<tr>
<td>- One person in chain of contact likely to be infectious (from catarrhal stage to 3 weeks after onset of cough)</td>
<td></td>
</tr>
<tr>
<td>- Laboratory evidence of pertussis in one of the cases</td>
<td></td>
</tr>
<tr>
<td>- Second person has onset of illness within 6–20 days after contact</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory investigation</strong></td>
<td></td>
</tr>
<tr>
<td>- If &lt;3 weeks of symptoms nasopharyngeal swab for culture and PCR, consider pertussis IgG serology</td>
<td></td>
</tr>
<tr>
<td>- If &gt;3 weeks since cough onset consider pertussis toxin IgG if available</td>
<td></td>
</tr>
</tbody>
</table>
Children

Children are more likely to experience ‘classical pertussis’, with an incubation period of 7–10 days (range 5–21 days), followed by three phases of illness:

- catarrhal – non-specific prodromal coryzal illness, mild cough, lasting 1–2 weeks
- paroxysmal – spasmodic cough, post-tussive vomiting and inspiratory whoop lasting 4–6 weeks
- convalescent – symptoms slowly improving over 1–2 weeks.

Complications are more common in non-immune infants. These include pneumonia, failure to thrive from post-tussive vomiting, seizures, encephalopathy, cerebral hypoxia, secondary bacterial infection, pulmonary hypertension, sub-conjunctival haemorrhage and rectal prolapse.22 Very young infants may initially present with apnoea alone. Most deaths from pertussis are in children under 6 months old, particularly in those under 1 month of age.54

Older children, adolescents and adults

Pertussis infection in older children, adolescents and adults can range from ‘classic pertussis’ to mild or no cough.29 In a recent UK study, 37% of consecutive children, aged 5–16 years, presenting to primary care with cough for more than 14 days had serological evidence of pertussis on well-standardised tests but culture or PCR were not routinely performed.55 While whoop and vomiting were significantly more common in children with serologic evidence of pertussis infection, and wheeze significantly less common, whoop was present in 25% of seronegative children and paroxysmal coughing in 75%. Coughing severity was greater in the seropositive group among whom 85% were still coughing 2 months later and significantly more had parents with sleep disturbance. It is important to note that children eligible for this study would have received their last dose of pertussis vaccine at 4 months of age but the UK now has a booster dose at 4 years. Despite this, seropositive children were significantly less likely to be completely vaccinated according to the UK schedule (86% vs. 97% of seronegative children).

Most cases of adult pertussis occur in those who have a history of past pertussis vaccination or infection.56 Pertussis has been found to be the cause in 13–20% of adults presenting with prolonged cough, although the nature of the referral population differs among studies.22 The mean duration of cough in adults with pertussis is 36–48 days and it may be only nocturnal.56 Adults and adolescents usually present late in the course of the infection, often after 4 or more weeks of coughing, although diagnostic delay by clinicians is also frequent.58 Complications in adults can also be severe including: hospitalisation, inguinal hernia, fractured ribs (<4%), carotid artery dissection, intracranial haemorrhage, pneumonia (<5%) and cough syncope (<6%). Death can occur, especially in the very elderly.22,53,59

Laboratory tests

Laboratory tests, including culture, serology and PCR, have varying sensitivity and specificity. Culture of B. pertussis is fastidious and has low yield except early in the course of infection. Serology is not useful in infants and in older persons is hampered by the limitations of paired sera, as no antibody rise may occur or collection may be too delayed to detect it. Neither method provides results as quickly as PCR, which must, however, be meticulously performed to avoid contamination. Specific details of each diagnostic method follow.

Culture

Culture is considered to be the gold standard, however, its sensitivity decreases steeply if the specimen is taken more than 2 weeks after onset of cough and is reduced by prior immunity from disease or immunisation. Three weeks after commencement of cough, sensitivity of culture is only 1–3%, even lower in adults and adolescents who are more likely to present late.53 However, culture allows typing and antibiotic sensitivity to be determined. Results can be available in 72 h, especially in high titre infection, such as in unimmunised infants, but 2 weeks are required before culture may be definitively reported as negative. The sensitivity of culture is reduced by the type of specimen collected (with a nasopharyngeal swab better than pernasal), the method of collection (preferably in younger children a nasopharyngeal aspirate) and the use of cotton or rayon swabs, which are inhibitory.22,53

Serology

Antibodies to different pertussis antigens – PT, PRN, filamentous haemagglutinin (FHA), fimbrial proteins and whole organism – appear following natural infection. Increases in anti-PT IgG and anti-FHA IgG are measurable in over 90% of infections, anti-PRN IgG in 30–60%, anti-PRN IgA in 20–40%, anti-PT IgA in 20–40% and anti-FHA IgA in 30–50% of infected persons.60 However, the antibody cut-off that defines a diagnosis of pertussis is debatable and somewhat test-dependent. The sensitivity of serologic tests tends to be lower than their specificity, ranging from 20%61 to 90%62 compared with culture and/or PCR.

Ideally acute sera (<2 weeks of illness onset) and convalescent sera (4 weeks post acute sera measurement) are obtained, however, serology is frequently used to diagnose infection late in the course of illness when acute sera have not been obtained. Serology, especially serum IgA, is not useful in children under 2 years old. Serology is
most useful in older children and adults, as delayed presentation makes other diagnostic methods – such as culture and PCR – less likely to be positive. As most adolescents and adults are partially immune from previous vaccination or infection, ideally two samples are needed to demonstrate a rise in antibody titre. The most specific serologic test is IgA or IgG to PT because it is unique to \( B. \) pertussis and decays to below cut-off levels most rapidly post infection, with an average of 4.5 months and in 82% of cases within 1 year of infection. For this reason, a single high IgG to PT has been used as a marker of acute pertussis infection with estimates of 76% and 99% for sensitivity and specificity respectively. In contrast, enzyme-linked immunosorbent assay tests that measure antibodies to whole pertussis antigens are less sensitive and specific.

Diagnosis based on single titre serology is more clinically useful. Investigators from the Netherlands found that a single serum with an anti-PT IgG of greater that 100 Dutch units/mL was indicative of recent (within 4 weeks) infection with \( B. \) pertussis proven by either a four-fold or higher change in the acute and convalescent sera, positive culture and/or PCR. Pebody et al. reported that a single serum mean anti-PT IgG antibody level equivalent to 125 ESEN U/mL was consistent with pertussis infection within six months of sample collection, while a level of >62.5 ESEN U/mL was consistent with infection within the past year. Currently only Australia, Finland and the Netherlands include serology based on single anti-IgA and/or anti-IgG antibody measurements in national pertussis notification data, in the former two using whole-cell based assays and in the Netherlands IgG to PT.

**PCR**

PCR is more sensitive than culture by 2- to 3-fold in patients who present after 3 weeks of coughing or commencement of antibiotic therapy. Reported sensitivities range from 73% to 100%. However, there is no inter-laboratory standardisation of PCR, with over 100 different PCR protocols reported, differing in DNA purification techniques, PCR primers, reaction conditions and product detection methods. The specificity of PCR can be reduced by contamination in the laboratory or at the time of specimen collection, such as false-positive PCR in patients with upper respiratory tract colonisation with \( B. \) holmesii. PCR does not cross react with \( B. \) parapertussis as this organism does not contain PT. The Center for Disease Control and Prevention (CDC) recommends that PCR be used to support the diagnosis of pertussis when the case meets the clinical case definition of 2 or more weeks of cough associated with paroxysms, whoop or post-tussive vomiting. However, strict application of this approach excludes contacts with no or lesser duration of symptoms where utility of PCR for diagnosis may be higher. PCR is particularly useful in infants where pertussis is suspected as serology is not applicable and specimens are more easily transported and more rapidly reported than for culture.

**MANAGEMENT**

**Acute pertussis infection**

Infection in infants under 6 months old may require hospitalisation for supportive care of complications, for example apnoea, hypoxia or feeding difficulties. Treatment with antibiotics does not significantly shorten the clinical course in infected patients but aims to reduce transmission to others. In the past, erythromycin was the first-line antibiotic for pertussis treatment but it was associated with significant adverse effects including hypertrophic pyloric stenosis in infants and cardiac arrhythmias (QT prolongation and ventricular arrhythmias). A recent Cochrane review recommended the use of azithromycin and clarithromycin as first-line antimicrobial agents. This is also supported by data from a multi-centre randomised trial in North America, where azithromycin was shown to be as effective as erythromycin, better tolerated and associated with improved compliance. The US CDC recommends that azithromycin should be used for all neonates under 1 month, with erythromycin, clarithromycin or azithromycin acceptable for the treatment of pertussis in persons aged ≥1 month. Resistance to azithromycin has been rarely reported. For treatment of persons aged ≥2 months, an alternative agent if there is allergy or intolerance to macrolides is trimethoprim-sulfamethoxazole (TMP–SMZ) although effectiveness is less well documented. Erythromycin and clarithromycin are inhibitors of the cytochrome P450 enzyme system (CYP3A subclass) and can interact with other drugs metabolised by this system. Azithromycin and clarithromycin are more resistant to gastric acid, achieve higher tissue concentrations, and have a longer half-life than erythromycin, allowing less frequent administration (1–2 doses per day) and shorter treatment regimens (5–7 days), with likely improved adherence to therapy. Roxithromycin is another macrolide antibiotic. However, there are no clinical studies on its effectiveness in pertussis, and in-vitro sensitivity studies suggest it may be inferior to erythromycin so it is not currently recommended for treating pertussis. Table 3 summarises the most common antibiotics used to treat acute pertussis and their regimen.

**Prophylaxis**

Macrolide antibiotics have been recommended for treatment of contacts within 3 weeks of onset of disease. In the US, contacts include all household members, and other close contacts, such as childcare attendees, regardless of their age and immunisation status. In the UK and Australia, more limited recommendations for treatment of contacts are made in view of the limited effectiveness of chemoprophylaxis, focussing on those at most risk of
complications. This includes any infant who has received less than three doses of DTPa, any woman in the last month of pregnancy and any child or adult who works/attends a healthcare or childcare facility.

Pertussis-containing vaccines should be given if due at the time of exposure or the course commenced in those who are unimmunised or not completely immunised. The Redbook 2006 recommends that children who have received their third dose more than 6 months prior to the exposure receive a fourth dose at the time of exposure. Children under 7 years of age who have had four doses where the last dose was more than 3 years before the exposure should also be given a DTPa vaccine. National guidelines from the UK and Australia also recommend DTPa vaccines be given to unvaccinated or partially vaccinated children who are contacts up to their 8th (Australia) or 10th (UK) birthday.

### CURRENT VACCINE STRATEGIES FOR PREVENTION

Vaccines using inactivated whole B. pertussis organisms (Pw) of three serotypes were first developed in the 1930s and subsequently combined with diphtheria and tetanus toxoids for widespread use in immunisation programs. In many industrialised countries currently acellular pertussis vaccines (Pa) that include up to five antigens, (PT, FHA, PRN and two different fimbrial proteins) are used. All manufacturers include PT and PRN as sub-studies from Pa efficacy trials have implicated PT and PRN, but not FHA, in protection and lead to the conclusion that PT and PRN IgG antibodies are the current best surrogate for protection. In many countries pertussis antigens are now included in multivalent vaccines, which may contain diphtheria, tetanus, hepatitis B, Haemophilus influenzae type B, and poliovirus.

Recently, a low dose, adult-formulated diphtheria, tetanus, acellular pertussis (dTpa) vaccine has been licensed and recommended in several countries, including the USA, Australia, Canada, France, Germany and Switzerland, for use in adults and adolescents. Efficacy data from a large trial in the USA (APERT), estimates vaccine protection from culture or PCR proven symptomatic pertussis disease is 92%, although protection against less severe coughing illness is likely to be only 50–60%.

### Potential strategies to address continuing pertussis in early infancy

Pertussis vaccination schedules differ significantly around the world but none currently start earlier than 6 weeks of age (Table 4). The WHO recommends a schedule of 6, 10 and 14 weeks for primary immunisation against pertussis. Re-evaluation of pertussis vaccination schedules is a priority given the resurgence of pertussis in very young infants and in those aged over 10 years. The Global

### Table 4 Pertussis vaccination schedules in selected countries

<table>
<thead>
<tr>
<th>Country/Organisation</th>
<th>Type of pertussis containing vaccine</th>
<th>Primary immunisation schedule</th>
<th>Adolescent dTp booster recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>DTPw</td>
<td>6, 10, 14 weeks</td>
<td>No</td>
</tr>
<tr>
<td>Australia</td>
<td>DTPa-combination</td>
<td>2, 4, 6 months</td>
<td>Yes</td>
</tr>
<tr>
<td>Brazil</td>
<td>DTPa-combination</td>
<td>2, 4, 6 months</td>
<td>No</td>
</tr>
<tr>
<td>Canada</td>
<td>DTPa-combination</td>
<td>2, 4, 6 months</td>
<td>Yes</td>
</tr>
<tr>
<td>Egypt</td>
<td>DTPa-combination</td>
<td>2, 4, 6 months</td>
<td>No</td>
</tr>
<tr>
<td>France</td>
<td>DTPa-combination</td>
<td>2, 4, 6 months</td>
<td>Yes</td>
</tr>
<tr>
<td>Germany</td>
<td>DTPa-combination</td>
<td>3, 5, 11 months</td>
<td>No</td>
</tr>
<tr>
<td>Italy</td>
<td>DTPa-combination</td>
<td>3, 5, 11 months</td>
<td>No</td>
</tr>
<tr>
<td>South Africa</td>
<td>DTPa-combination</td>
<td>6, 10, 14 weeks</td>
<td>No</td>
</tr>
<tr>
<td>Sweden</td>
<td>DTPa-combination</td>
<td>3, 5, 12 months</td>
<td>Yes</td>
</tr>
<tr>
<td>UK</td>
<td>DTPa-combination</td>
<td>2, 3, 4 months</td>
<td>No</td>
</tr>
<tr>
<td>USA</td>
<td>DTPa-combination</td>
<td>2, 4, 6 months</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Available at: [http://www.who.int/immunization/en/](http://www.who.int/immunization/en/).
Pertussis Initiative (GPI) – a multidisciplinary panel of experts created in 2001 – recently evaluated seven potential pertussis vaccine strategies. These strategies, which are not mutually exclusive, include: universal adult and/or adolescent vaccination; indirect protection of infants by immunisation of parents and possibly others in close contact with the newborn, such as grandparents and healthcare workers; infant and early infant immunisation (from birth to 1 month of age); and maternal immunisation.

**Adult/adolescent vaccination**

A reduction in the adult/adolescent reservoir could be achieved by administering a booster dose of DTPa. Universal vaccination for adolescents is recommended in several countries (Table 4).

**Indirect protection of infants through parental vaccination**

There is good evidence that parents are the most common source of infection for infants and that dTpa booster vaccine given to parents can prevent or reduce adult infection rates. In Australia, France, Germany, the USA and Austria it is recommended that all parents of newborns receive a dTpa booster shortly after delivery of their child. Modelling has demonstrated that a combination of routine adult vaccination every 10 years commencing at age 20 years and selective vaccination of household contacts of newborns would result in the greatest reduction in infant pertussis incidence. Another modelling study suggested that the combination of a cocoon strategy and a single dose for all adults might be easier to implement than recurrent doses for adults.

**Earlier infant and neonatal immunisation**

Recently attention has turned to whether acellular pertussis vaccines could be administered to infants earlier than 6–8 weeks old. There are three reported human studies, only two published, reporting the effect of Pa vaccination at birth. First, an Italian study showed that a birth dose of Pa vaccine followed by doses containing the same amounts of pertussis antigens at ages 3, 5 and 11 months, resulted in earlier antibody responses compared with the standard Italian schedule for DTPa vaccination at 3, 5 and 11 months. Second, a US study compared DTPa administered at birth in 50 term infants with the standard vaccination schedule. Pertussis antibody levels were similar at 6 months of age in the two groups, but at 7 months levels were significantly lower in the group vaccinated at birth, suggesting that birth vaccination may result in earlier antibody loss and that additional boosters may be required after 6 months. Third, a German study found Pa vaccine at birth resulted in a significantly higher response to pertussis antigens at 3 months of age compared with controls but no difference at 7 months of age. No significant adverse events were reported following neonatal Pa vaccination in these three studies, however neonatal vaccination may be associated with potential alterations in immune responses to other vaccine antigens (diphtheria, tetanus, Hepatitis B) co-administered with the Pa vaccine.

**Maternal vaccination during pregnancy**

Maternal vaccination has been extremely successful in preventing neonatal tetanus in developing communities. Maternal pertussis immunisation is a possible strategy for prevention of infant infection, because active placental transfer of pertussis specific antibodies to the foetus occurs and has been recently reviewed. No studies evaluating antibody response or protection following maternal vaccination with acellular pertussis vaccines in pregnancy are currently available.

**INTERNATIONAL COLLABORATIONS**

International collaborative efforts to address the rising incidence of pertussis have commenced. The GPI was created in 2001, following an educational grant from Sanofi Pasteur, and includes over 30 scientific experts from 17 countries who were divided into three regional subgroups – Europe, North America and International. The focus of this group is to raise global awareness of pertussis as an important preventable disease and to develop and communicate evidence-based recommendations for immunisation based strategies to slow the increasing trend in pertussis incidence. For many resource-poor settings, an accurate estimate of the true burden on pertussis is not known, access to new diagnostic methods, such as PCR, is non-existent and problems with vaccine availability result in low coverage in some areas, although overall global coverage for three doses of pertussis vaccine has now reached 80%. Attempts to improve vaccine coverage through international groups, such as the Gates Foundation, and newer methods of financing (International Financing Facility) will assist in improving coverage. However, measuring the impact of vaccination on reducing pertussis disease burden will require high quality epidemiological data and support for the development of monitoring systems in resource-poor settings is needed. In addition, improvements in the sensitivity and specificity of laboratory diagnostic methods, technology transfer to resource poor settings, could result in earlier more accurate diagnosis, earlier commencement of treatment and reduced transmission. One of the UN Millennium Development Goals is to reduce child mortality by one-third by 2015 and includes the necessity to reduce pertussis deaths.
CONCLUSION

Globally, pertussis remains a challenge in both developing and developed countries. In both settings, infants under 5 months of age have the highest rates of pertussis disease, morbidity and death. In developed countries widespread universal vaccination of infants has dramatically decreased the incidence of pertussis, especially hospitalisation and death, among those aged 1–10 years, but the burden of disease has shifted to older ages with adolescents and adults now most likely to transmit pertussis to a young infant. In developing countries, high coverage for three doses of pertussis-containing vaccines at 6, 10 and 14 weeks remains the key challenge and transmission from older children is still the primary issue. The management of suspected pertussis requires a combination of clinical suspicion, laboratory tests based on age and clinical history, antibacterial therapy for cases and, where appropriate, for contacts. PCR and single titre serology are more useful than culture when confronted with patients coughing for 1–3 weeks (PCR) and for more than 3 weeks (serology) or in those with preceding antibiotic therapy. Antibacterial therapy makes a minimal contribution to the control of pertussis, with better and wider use of vaccines the most important strategy in developed and developing countries.

KEY POINTS

- In countries with well-developed immunisation programs, symptomatic pertussis infections are now predominantly in the least well-immunised groups (over the age of 10 years and under 5 months).
- In adults and older children, diagnosis of pertussis is often delayed because classic symptoms are frequently absent, resulting in the potential to transmit infection for several weeks.
- The sensitivity of laboratory tests for pertussis is reduced by the use of antibiotics early in the course of infection, mixed infections, delay in presentation and/or diagnosis inherent limitations. Available tests are predominantly serology, PCR and culture:
  - nasopharyngeal swab for culture and/or PCR has highest yield <2 weeks after cough onset, unlikely to be positive >3 weeks
  - serologic tests are best standardised for IgG to PT; single titre serology only feasible diagnostic test 3 or more weeks after cough onset.
- Antibiotic treatment does not significantly shorten the clinical course in infected patients but aims to reduce transmission to other persons. Azithromycin is the agent of choice but expensive.

REFERENCES

CME SECTION

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Educational questions

Answer true or false to the following questions:

1. With regard to the current epidemiology of pertussis in countries with well-developed immunisation programs:
   a. Pertussis infection is predominant in children aged 1–5 years old.
   b. The high rates in adolescents and adults are primarily due to waning immunity.

2. With regard to the diagnosis of pertussis:
   a. The sensitivity of culture increases steeply if the specimen is taken more than 2 weeks after onset of cough.
   b. Sensitivity of culture is increased with the use of swabs taken by the pernasal route.
   c. The most specific serologic test is IgA or IgG to PT, which is unique to B. pertussis.
   d. Individuals with pertussis disease are most infectious when spasmodic cough is established.
   e. Polymorphism of pertussis genes is induced by vaccination programs and the main cause of the rising pertussis incidence.
   f. Pertussis has been found to be the cause in up to 20% of adults with prolonged cough in countries with well-developed immunisation programs.

Infants under 5 months old are reliably protected from pertussis infection by current vaccination schedules.

Individuals with pertussis disease are most infectious when spasmodic cough is established.

Polymorphism of pertussis genes is induced by vaccination programs and the main cause of the rising pertussis incidence.

Pertussis has been found to be the cause in up to 20% of adults with prolonged cough in countries with well-developed immunisation programs.

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   a. The sensitivity of culture increases steeply if the specimen is taken more than 2 weeks after onset of cough.
   b. Sensitivity of culture is increased with the use of swabs taken by the pernasal route.
   c. The most specific serologic test is IgA or IgG to PT, which is unique to B. pertussis.
   d. A single IgG titre to PT has a sensitivity of approximately 75% for acute pertussis infection.
   e. PCR is less sensitive than culture in patients who present after commencement of antibiotic therapy.
f. False-positive PCR can occur in patients with upper respiratory tract colonisation with *Bordetella holmesii*.

3. Pertussis treatment
   a. Treatment with antibiotics shortens the clinical course in infected patients by about 2 weeks.
   b. Azithromycin and clarithromycin are currently recommended as the first-line antimicrobial agents.
   c. An advantage of erythromycin is improved compliance due to a reduced duration of therapy.
   d. Alternative agent to macrolides is trimethoprim-sulfamethoxazole (TMP–SMZ) in the case of allergy or intolerance.
   e. Macrolide antibiotics have been recommended for treatment of contacts within 8 weeks of onset of disease in the case.
   f. Pertussis containing vaccines should be given if due at the time of exposure or the course commenced in those who are incompletely immunised.

4. With regard to pertussis vaccination strategies:
   a. Currently, acellular pertussis vaccines (Pa) all include the antigens PT, FHA, and fimbrial endotoxin.
   b. Estimates of vaccine protection from low dose dTpa booster vaccine in adults are over 90% for culture or PCR proven symptomatic pertussis.
   c. Parents of newborn infants are recommended to receive a booster dose of low dose dTpa vaccine.
   d. Neonatal administration of acellular pertussis vaccine is now routinely recommended in several countries.
   e. Women should never receive dTpa vaccine while pregnant.
   f. National guidelines on vaccination regimens exist in many countries and are available for clinician use.