Introduction

Despite substantially improved disease prevention since the introduction of universal infant vaccination, pertussis (whooping cough) is one of the leading causes of vaccine-preventable deaths. Worldwide, an estimated 50 million cases of disease and 300 000 deaths occur every year. Although developed countries have generally achieved high rates of vaccination coverage in infants, the effect on circulating Bordetella pertussis has been limited, which is mainly attributable to waning immunity occurring 4–12 years after vaccination or 4–20 years after natural infection.

The belief that pertussis is chiefly a childhood disease is a common misconception. Whereas disease incidence in young children has been declining since the introduction of vaccination in paediatric age groups, the number of reported cases across all other age groups has increased in many European countries during the past decade. In particular, the incidence of pertussis in adolescents and adults has increased in Europe and the USA and these groups are now the main reservoir of infection (figure 1). This changing epidemiological pattern contributes to ongoing challenges for disease control. The apparent resurgence in pertussis might also be related to an increased awareness of the disease after the introduction of improved diagnostic tests and more active surveillance. Furthermore, changes in disease susceptibility and vaccine characteristics, shifting demographics, variations in vaccination coverage, and genetic variations of B pertussis could influence pertussis incidence. Untreated, pertussis is highly contagious during the first few weeks of onset of disease symptoms, and one primary case can lead to 11–17 secondary cases in an immune-naïve population. Because the clinical presentation of pertussis in adolescents and adults often goes unrecognised, the potential for disease transmission and risk of outbreaks in susceptible populations is high.

In this Review, we assess the present pertussis situation with a specific focus on Europe and detail considerations for booster vaccinations in different age groups.

The Consensus on Pertussis Booster Vaccination in Europe initiative

In Europe, pertussis vaccination schedules vary between countries, and although many schedules routinely include booster vaccinations for preschool children, recommendations for adolescents and adults are less common and immunisation uptake is low in these groups (table 1). Recognising the need for pan-European guidance, a panel of European experts met in 2008 and 2009 to discuss and share evidence and expert opinions about clinical and biological diagnoses, epidemiology, and vaccination needs for pertussis across Europe. The meetings led to the development of a series of proposals about the use of pertussis booster vaccinations in different age groups that are reported in this Review.

Burden of pertussis

Morbidity and mortality associated with pertussis decreased substantially after the introduction of vaccination programmes, however, hospital admissions and fatalities are still evident, particularly in young infants. Pertussis-related case-fatality seems to be inversely associated with age, with most deaths occurring in unvaccinated or incompletely vaccinated infants who are younger than 12 months. In a retrospective analysis of 100 deaths attributable to community-acquired bacterial infection in children aged 10 days to 18 years in France, B pertussis caused 13% of all deaths, all of which occurred in children younger than 2 months. Reported complications of pertussis in adolescents and adults include sinusitis, otitis media, urinary incontinence, pneumonia, weight loss, rib fractures, encephalopathy, and fainting. Furthermore, underlying respiratory conditions might be worsened by pertussis. For example, investigators in one study reported that almost a third of adults (31%) with acute exacerbations of chronic bronchitis were also infected with B pertussis.

Pertussis also affects the patient’s family; for example, parents worry and lose sleep when caring for a child with the disease and might lose workdays or be less

Rationale for pertussis booster vaccination throughout life in Europe

Fred Zepp, Ulrich Heininger, Jussi Mertsola, Ewa Bernatowska, Nicole Guiso, John Roord, Alberto E Tozzi, Pierre Van Damme

Although the introduction of universal pertussis immunisation in infants has greatly reduced the number of reported cases in infants and young children, disease incidence has been increasing in adolescents and adults in recent years. This changing epidemiological pattern is probably largely attributable to waning immunity after natural infection or vaccination. Furthermore, improved diagnostic testing, active surveillance, changes in disease susceptibility, vaccine characteristics, and increased awareness of the disease might also be contributing factors. Susceptibility to pertussis in adolescents and adults results not only in direct morbidity in these age groups, but also poses a transmission risk to susceptible non-immune infants who are often too young to be vaccinated. Because vaccination schedules vary across Europe, we review the pertussis situation in this region and propose considerations for use of pertussis booster vaccinations at different ages to reduce individual morbidity and transmission from present rates and increase herd protection.

Introduction

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Pertussis also affects the patient’s family; for example, parents worry and lose sleep when caring for a child with the disease and might lose workdays or be less
productive at work than normal. In addition to the burden placed on individuals and families, the broad socioeconomic burden of pertussis is notable. During an outbreak in France, more than half of 77 health-care workers with suspected infections missed 5 days of work and this lost productivity accounted for about 42% of total costs.

Epidemiology and surveillance across Europe

Epidemiological data collection varies between countries via surveillance of the general population, sentinel surveillance systems, voluntary notifications from healthcare providers, and laboratory notification. France employs a paediatric hospital-based surveillance system (Renacoq, established in 1996) for disease monitoring, with additional information provided by voluntary reporting from family doctors and mandatory nosocomial infection reports. Reporting of pertussis infection in Sweden has been obligatory since 1997 and clinically suspected or laboratory-confirmed cases are reported to the Swedish Institute for Infectious Disease Control.

Table 2 summarises characteristics of other European surveillance systems.

Diagnostic methods applied and case definitions for surveillance are also variable and include use of the WHO clinical case definition (panel 1), laboratory confirmation or an epidemiological link to a confirmed case, local case definitions, or doctors’ clinical diagnoses.

The European-wide programme, EUVAC-NET, was initiated in 1998 and funded by the European Community for the surveillance of vaccine-preventable diseases. During the 5 years between 1998 and 2002, 72,917 cases of pertussis were reported in 16 countries. The distribution of cases varied considerably between countries, with the highest number of cases reported by the Netherlands, Italy, Norway, Sweden, and Germany. This variation probably stems from differences in national surveillance systems, accessibility to sensitive diagnostic procedures, vaccination schedules, vaccines used, and vaccine coverage.

During the subsequent 5 years (2003–07), 43,482 cases of pertussis were reported in 20 European countries (table 3), equating to an incidence of about 4-1 per 100,000 people per year. Although various different countries participated in this second phase of the EUVAC-NET project, a general trend towards a higher proportion of cases in older individuals has been reported over time (figure 1).

Disease incidence is probably higher than surveillance data suggest due to underconsulting, under-recognition.
or misdiagnosis, and under-reporting of the disease. A study in the UK undertaken between 1994 and 1996 suggests that incidence of pertussis might be about three-times higher than official notification rates. Similarly, estimates of pertussis incidence in Italy collected from a paediatric sentinel network were three-times to seven-times higher than those obtained through statutory notifications. Although surveillance systems involving only paediatricians have been employed (eg, Cyprus), studies suggest that adults and especially elderly family members are an important source of infection and should be covered by pertussis surveillance systems. In France, 70 (32%) of 217 adults who consulted their family doctor for a persistent cough without an evident cause were infected with *B pertussis*. In another French regional study the annual incidence of confirmed pertussis, as assessed through monitoring of adolescents and adults who consulted their family doctor for persistent cough, was estimated to be 145 cases per 100,000 habitants. Furthermore, in an international prospective study undertaken in France and Germany, household members including parents, siblings, and grandparents were the source of 76–83% of laboratory-confirmed cases of infant pertussis.

The Consensus on Pertussis Booster Vaccination in Europe (COPE) group proposes that more extensive standardisation of European surveillance systems would help provide a clear description of pertussis epidemiology. The first steps towards such standardisation could include universal adoption of a common case definition (eg, the WHO pertussis case definition), standardisation of laboratory diagnostic methods, and surveillance of the general population rather than selected populations of patients or age groups.

### Diagnosis of pertussis

Routine clinical diagnosis of pertussis is complicated by various factors including variations in clinical presentation, age, previous exposure to *B pertussis* (ie, infection or immunisation), antibiotic therapy and,

<table>
<thead>
<tr>
<th>Type of data provided</th>
<th>Type of surveillance</th>
<th>Population coverage</th>
<th>Recommended case definition</th>
<th>Laboratory methods available for case confirmation</th>
<th>Minimum requirement for case notification</th>
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<tr>
<td>Belgium</td>
<td>Case-based</td>
<td>Passive reporting and sentinel laboratory surveillance system</td>
<td>100%</td>
<td>Clinical case with laboratory confirmation</td>
<td>Culture and PCR</td>
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<tr>
<td>Finland</td>
<td>Case-based</td>
<td>Passive</td>
<td>100%</td>
<td>Laboratory confirmation</td>
<td>Culture, PCR, and serology</td>
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<tr>
<td>France</td>
<td>Case-based</td>
<td>Hospital-based and paediatrician sentinel network (ACTIV)</td>
<td>43 hospitals across the country and 54 paediatricians</td>
<td>3 weeks of cough, or 1 week of typical cough with confirmation by laboratory or EpiLink</td>
<td>Culture, PCR, and serology</td>
</tr>
<tr>
<td>Germany</td>
<td>Case-based</td>
<td>Passive</td>
<td>100%</td>
<td>Clinical diagnosis with laboratory confirmation</td>
<td>Culture, PCR, and serology</td>
</tr>
<tr>
<td>Italy</td>
<td>Case-based</td>
<td>Universal</td>
<td>100%</td>
<td>Clinical diagnosis of pertussis</td>
<td>Culture and commercial serology diagnostics</td>
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<tr>
<td>Italy</td>
<td>Aggregated</td>
<td>Sentinel</td>
<td>5% of children 0-14 years</td>
<td>Clinical diagnosis</td>
<td>Culture and commercial serology diagnostics</td>
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<td>Netherlands</td>
<td>Laboratory and clinical notification</td>
<td>100%</td>
<td>Serious cough &gt;14 days, coughing attacks, or cough followed by vomiting with positive bacteriological or serological findings in the patient, or in the index patient</td>
<td>Culture and/or PCR</td>
<td>Positive serology</td>
</tr>
<tr>
<td>Poland</td>
<td>Case-based</td>
<td>Universal</td>
<td>100% of children 0-18 years</td>
<td>Clinical diagnosis of pertussis</td>
<td>Commercial serology diagnostics</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Clinical data, ambulatory setting</td>
<td>Sentinel surveillance system</td>
<td>Approximately 3.5% of total population, all age groups</td>
<td>Cough &gt;14 days with either an epidemiological link to another pertussis case (epidemic case), or with one of the following symptoms: paroxysmal cough, wheezing inspiration or post-tussive vomiting (sporadic case)</td>
<td>PCR</td>
</tr>
</tbody>
</table>

Information was provided by the EUVAC-NET study group and the authors of this Review. ACTIV=Association Clinique Thérapeutique Infantile du Val de Mar.

### Table 2: Examples of pertussis surveillance systems in Europe

Panel 1: WHO pertussis case definition

**Clinical case**

- Patient diagnosed with pertussis by a doctor
- Patient with a cough lasting at least 2 weeks with at least one of the following symptoms:
  - Paroxysms of coughing
  - Inspiratory whooping
  - Post-tussive vomiting without other apparent cause

**Laboratory confirmation**

- Isolation of *Bordetella pertussis*, or
- Detection of genomic sequences with PCR, or
- Positive–paired serology

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possibly, concomitant infections. By contrast with the prevaccine era, atypical disease (often characterised by the absence of paroxysms and whoop) is noted more commonly today than are classic symptoms, especially in adolescents and adults. Data show that most pertussis infections in adults and adolescents are actually asymptomatic or oligosymptomatic, with the ratio of asymptomatic to symptomatic infections varying from 3·5 to 1·0 to 21·6 to 1·0.

Despite improvements in recent years, biological diagnosis of pertussis is challenging, with the requirement of specific sampling techniques and the limited availability of laboratory testing potentially contributing to under diagnosis or misdiagnosis. Two approaches are employed to detect bacteria in nasopharyngeal specimens: bacterial culture and PCR. Bacterial culture is highly specific and allows antibiotic susceptibility testing, but has low sensitivity (which declines with disease duration) and takes several days to complete. Real-time PCR is more rapid and significantly more sensitive, although sensitivity also decreases with illness duration, and false-positive results might occur in the absence of stringent laboratory quality-control measures. Additionally, use of serology necessitates consideration of recent immunisation history, which might complicate assessment of the results. Indeed, more rapid increases and decreases of anti-pertussis toxin IgG antibody titres are noted in vaccinated groups than are in unvaccinated groups. This finding is likely to be of increasing importance if adolescent and adult booster vaccines become more widely used. In general, commercially available assays employ different antigens and require different interpretations; so far, none of the available assays has been validated. ELISA determination of serum antibody titres can be established with single-serum or paired-serum samples (ie, taken at different

Serological diagnosis relies on determination of changes in the concentrations of B pertussis-specific antibodies in infected individuals. Although culture and PCR can be used early in the course of the disease, single-specimen serology is employed late in the course as serum antibodies do not usually peak until 3 weeks after the onset of cough. Although the kinetics of the immune response to pertussis infection vary between individuals, antibody titres (eg, pertussis toxin antibody) generally increase during the first few weeks after onset of cough and then decline during the convalescent phase. Observation of this pattern supports consideration of decreased antibody concentrations as part of the diagnostic process.

Asymptomatic to symptomatic infections varying from 3·5 to 1·0 to 21·6 to 1·0.

Table 3: Number of reported cases of pertussis and laboratory-confirmed cases, 2003–07

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Data are n or n (%). Data from reference 4. NA=not available. *Reported aggregated data for 2003–07. †Reported partly aggregated data for 2003–07.
times to assess the change in concentrations). Paired-sample serology is less practical for routine diagnosis and single-sample serology has therefore been the focus for a number of laboratories that assessed various cutoff levels. For example, a serum IgG titre of 100 U/mL or more against pertussis toxin has been regarded as indicative of recent or active pertussis infection in the Netherlands and the UK. This measure of seropositivity was employed as a comparator in a study in the UK, which investigated the potential of oral sampling as an alternative method to serum collection in young children. The investigators concluded that oral fluid anti-pertussis toxin IgG titres of 70 arbitrary units or more provided a relatively high positive predictive value of 76·2–93·2% for pertussis in children with chronic coughs.

There are several barriers to early diagnosis of pertussis. Symptoms of pertussis vary from mild respiratory symptoms to full-blown disease with characteristic paroxysmal coughing, inspiratory whooping, choking, and sometimes vomiting. Clinical symptoms that are predictive of pertussis include paroxysmal or severe prolonged cough, post-tussive vomiting, whoop, and obstructive apnoea, in addition to a long interval since the last pertussis vaccination.

The disease course can be influenced by various factors including immunisation history, age and sex of the patient. For example, women have been reported to present with more vomiting, whooping, and paroxysms than have men, whereas a study of children younger than 6 years of age reported the duration of spasmodic cough to be longer in girls than in boys. Such variation in presentation complicates or delays diagnosis, especially in adolescents and adults. Atypical presentation of pertussis is increasingly common, with a persistent cough often the only sign to suggest the presence of the disease. However, coughing is a commonly encountered symptom in the general population and might be attributed to a number of underlying causes. Because vaccination programmes in infants and in early childhood are well established, pertussis is often thought to be low on the list of suspected infections and frequently goes unrecognised or misdiagnosed. Pertussis might be misidentified as *Mycoplasma pneumoniae*, sinusitis, or upper respiratory tract infection. A study of schoolchildren aged 6–14 years with persistent cough in a region of Turkey, reported that 16–6% had serological evidence of a recent pertussis infection despite no cases having been diagnosed by a doctor. One epidemiological review suggested that rates of reported pertussis could be 40-fold to 160-fold lower than were actual disease rates. Furthermore, a study done in the Netherlands reported that pertussis infection rates, as noted by serological analysis were 685-times higher than were notified infections (6·6% vs 0·01%, respectively) for people aged 3–79 years.

Presently, optimum rates of pertussis diagnosis are restricted by two key issues: first, a mistaken and perhaps widespread belief that this disease is controlled by contemporary vaccination programmes, and second, underestimation of clinical symptoms, especially in adults, by health-care providers. Raising of awareness among these providers and the general population to consider the possibility of pertussis for individuals with persistent cough is one of the steps to better recognition.

Early accurate diagnosis is important to control transmission of the disease and to enable prompt antibiotic treatment. Because atypical presentation is more common...
at present than it was in the prevaccination era, a shift away from pure reliance on clinical diagnosis and a move towards more regular laboratory testing is needed.\textsuperscript{35}

The optimum diagnostic method according to age, immunisation, and duration of cough needs to be established. Accurate clinical and biological diagnoses of pertussis are challenging to make, and false-negative and false-positive results can occur. Panel 2 provides an overview of key considerations for diagnosis of pertussis. In terms of biological confirmation, culture, PCR, and serology continue to have prominent places in the diagnostic process, but all have limitations, and their use is dependent on the age and history of the patient (panel 2). A standardisation of diagnostic methods is urgently needed throughout Europe.

**Pertussis booster vaccines**

Pertussis vaccination schedules vary between countries; however, after primary vaccinations during infancy (usually three consecutive doses after the second month of life), a booster vaccination is usually given in the second year of life in addition to a preschool booster in many countries (table 1). Thereafter, only a few countries have introduced booster doses for adolescents (eg, Austria, Belgium, Finland, France, Germany, and Italy) and adults (eg, France and Germany).

Several vaccines are available for boosting immunity to pertussis. The immunogenicity of the combination tetanus–diphtheria acellular pertussis vaccine (dTpa) with or without inactivated poliovirus as a booster dose has been shown in studies of preschool children (aged 4–7 years) and young adolescents (aged 11–13 years) irrespective of vaccination history.\textsuperscript{56–58} Reactogenicity was considered acceptable (the most common adverse events being pain, redness, and swelling) and was lower than that associated with fourth or fifth doses of combined tetanus–diphtheria whole-cell pertussis vaccine (DTPw).\textsuperscript{62} Duration of protection seems to be broadly the same between acellular and whole-cell pertussis vaccines (≥4 years postvaccination).\textsuperscript{3} In most industrialised countries, acellular vaccines have now replaced whole-cell vaccines.

Combined reduced antigen content tetanus–diphtheria and acellular pertussis vaccines (dTPa) were first introduced for booster vaccination of adolescents and adults to help to reduce reactogenicity. Although these vaccines contain lower quantities of component antigens than do primary doses of pertussis vaccines, immunogenicity is unaffected.\textsuperscript{3} Commercially available vaccines include Boostrix (a three-component vaccine produced by GlaxoSmithKline Biologicals, Rixensart, Belgium), Repevax (a five-component vaccine produced by Sanofi Pasteur, Lyon, France), and Pediacel (a five-component vaccine produced by Sanofi Pasteur).

Data from studies\textsuperscript{60–68} of several thousand adolescents and adults have shown the immunogenicity, safety, and acceptable reactogenicity of dTpa booster vaccination (with or without inactivated poliovirus). Many of these studies also directly support the non-inferiority of the combined dTpa vaccine compared with reduced antigen content tetanus–diphtheria vaccine (dT) and acellular pertussis vaccines in terms of immunogenicity and adverse-event profiles in these age groups.\textsuperscript{60–68} A month after vaccination, high rates of seroprotection and seropositivity to all antigens (diphtheria and tetanus antigens ≥0·1 IU/mL and pertussis antigens ≥5 U/mL on ELISA) were reported with a seroprotection rate of more than 93% for diphtheria and tetanus and seropositivity of more than 98% for pertussis antigens in adults.\textsuperscript{64} Because there is no clear serological correlate of protection for pertussis antigens, immunogenicity is assessed by seropositivity and vaccine response (ie, seroconversion in previously seronegative individuals or a more than twofold increase in prevaccination titres in seropositive individuals).

Although the frequency of local injection-site reactions has been noted to increase in children receiving a fourth or fifth dose of DTPa, a study investigating dTpa (simultaneously with hepatitis A vaccine) as a sixth acellular pertussis-containing dose in adolescents showed that this outcome of increasing reactogenicity was reported for injection-site pain only.\textsuperscript{62} Reassuringly, a low prevalence (0·94%) of large injection-site swelling was seen in this study, which was consistent with the findings of a large study of dTpa vaccination in adolescents in the USA.\textsuperscript{61}

Long-term persistence (up to 5 years after combined dTpa) of seroprotection to diphtheria and tetanus has been shown in adolescents and adults, with much the same results as were noted in long-term follow-up after dT vaccination.\textsuperscript{69–71} Pertussis antibodies also remained detectable after 5 years of follow-up in most patients.\textsuperscript{69–71} Such study results support the replacement of dT with dTpa, because the combined booster vaccine has equivalent protection against diphtheria and tetanus with additional boosting of pertussis immunity.

Mathematical modelling of 5-year follow-up data from a dTpa trial in adolescents\textsuperscript{63} predicted that antibody decay would reach prevaccination rates between 9·5 and 15·0 years for the different pertussis antibodies, a finding which supports proposals for decennial boosting to replace present dT schedules.\textsuperscript{72} Long-term vaccine trials are underway to further validate the findings from these mathematical modelling studies.

 Provision of a dTpa booster dose to adolescents who had previously not received a pertussis vaccination and had no history of pertussis led to an IgG immune response up to 49 days to pertussis toxoid in 88·6% of patients, to filamentous haemagglutinin in 91·9%, and to pertactin in 96·7%.\textsuperscript{73} These results suggest that one dTpa booster dose can be used in adolescent or adult populations with no history of pertussis disease or vaccinations.

In the following sections, we review the strategies available to countries wishing to improve their present pertussis immunisation programmes. Although these strategies could be implemented individually, they

\textsuperscript{562}
should be viewed as complementary and adoption of more than one approach to pertussis booster vaccination would make the most of opportunities to increase herd protection.

Cocooning immunisation strategy
Cocooning focuses on protecting newborn infants against pertussis by vaccination of family members and other adults in close contact with the infant. Studies report that family members (parents, grandparents, and siblings) can be the source of infection in newborn babies and young infants in a substantial proportion of cases (>33%) when an infection source could be identified.36,53,75 Health-care workers can also be a source of infection when clusters of cases are reported in health-care settings.29 Molecular typing of B pertussis isolates recovered from Belgian children and their household members confirmed that identical strains can cause full pertussal disease in children and asymptomatic infection in adults and adolescents.76

The COPE group therefore propose that adults (eg, parents, grandparents, child-care providers, and health-care providers) who have or who expect to have close contact with a non-immune or incompletely vaccinated infant who is younger than 12 months should receive a single dose of dTpa if they have not received dTpa within the previous 10 years. The updated WHO pertussis position paper77 also supports booster vaccination of health-care workers (especially those in maternity and paediatric units) in countries that have a high rate of nosocomial transmission. A cost-effectiveness analysis undertaken in the Netherlands concluded that a cocooning immunisation strategy (for new parents) would be cost effective, and from a societal perspective, might even be cost-saving. The base-case analysis also suggested a reduction in the overall number of cases of pertussis in infants by 26%, although in this case infants would still be susceptible to transmission from other family members, such as the grandparents. In terms of immunisation of an elderly population,79 an Austrian study investigated the effect of a dTpa-inactivated poliovirus booster given to healthy adults (252 adults, median age 66 years). 5 weeks after vaccination, a humoral immune response was noted to the vaccine components. The magnitude of response, however, was influenced by prevaccination antibody titres, with patients who had lower prevaccination titres showing reduced responses. The study investigators note that routine booster programmes would be beneficial to avoid loss of humoral protection.

Post-partum women are regarded as the most important group to immunise to protect newborn babies. In line with the US Centers for Disease Control and Prevention (CDC) recommendations, an initiative in the USA has been introduced to implement a standing protocol of dTpa immunisations to post-partum women before hospital discharge.80 Of the targeted population, 72% received the booster dose, with various reasons given for those who were not immunised, such as those who had recently received a dTpa immunisation. Provision of appropriately tailored education to nurses, doctors, and patients was identified as key to gaining support for the initiative, with nurses becoming powerful advocates for vaccination during the study.80 In the USA, the Advisory Committee on Immunization Procedures recommends that where possible women and their partners receive a dTpa booster before pregnancy as part of preconception planning.81 These recommendations also state that women of childbearing age should be a focal point for dTpa booster doses so that protection is provided in the event of unplanned pregnancy. Much the same recommendations have been made in Germany and France.82,83 The question of whether pertussis booster vaccination during pregnancy is viable or advisable is still under investigation. Although vaccination during pregnancy could potentially protect both mother and newborn baby, more data are needed for the extent of antibody transfer to the unborn child, the safety of such an approach, and whether there would be any implications for the infant’s subsequent primary immunisation schedule.

Whereas a cocoon strategy could have a small effect on the number of cases of adult pertussis, it can have a strong indirect effect on infants and young children if high rates of coverage can be achieved.28,45 Therefore, it is proposed that the cocoon strategy (ie, vaccination of close-contacts to newborns with dTpa) should continue and be further promoted until immunisation coverage in adults is sufficient for herd protection.

Immunisation in preschool children
Provision of booster vaccinations to preschool children would increase herd immunity and reduce rates of disease transmission to infants and neonates.86 Additionally, preschool booster vaccination might also reduce morbidity caused by pertussis in children up to the age of 8–12 years. Furthermore, if such preschool booster vaccination were linked to a school health system or other accessible public health system, coverage would be improved.

Use of a pertussis booster vaccination in preschool children may prevent more cases of pertussis than the primary immunisation schedule alone. Epidemiological data from various countries or regions suggest waning immunity of primary infant pertussis vaccinations and positive effects of preschool booster vaccinations.75-84 An epidemiological assessment of pertussis in different regions of Germany reported a substantially increased incidence in children aged 5–14 years in a German state (Mecklenburg-Vorpommern) that did not advocate preschool boosters until 2006 compared with a state that did (Saxony; figure 2).84 Mecklenburg-Vorpommern introduced a preschool booster vaccination in 2005.

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In the Netherlands, the introduction of an acellular booster vaccination for children aged 4 years in 2001 substantially decreased disease incidence in the targeted population. Furthermore, incidence also declined in young infants, suggesting an indirect protective effect of the preschool booster. This latter observation suggests the potential transmission risk from this age group to susceptible young siblings.

**Immunisation in adolescents**

Several countries in Europe presently include a recommendation for pertussis booster vaccination in adolescents (table 1), although the age window varies between countries. Australia, the USA, and Canada have also included adolescent boosters in their vaccination schedules. Immunisation coverage in this age group is, however, modest or insufficient (~40% coverage in the USA).

Globally, evidence is accumulating to suggest a need for pertussis booster vaccination in adolescents. Alongside findings from EUVAC-NET, additional data from countries such as France, Germany, and Poland and data from the USA and Canada show increasing incidence of pertussis in adolescents and adults. Indeed, the fastest increase in incidence in the USA has been reported in adolescents (62% between the 1995–96 and 1997–2000 CDC surveillance data). This pattern continued with the 2001–03 CDC data, showing the largest proportion of cases (33%) occurred in 10–19 year olds. An epidemiological review of studies from the 1980s and 1990s suggested that about 13% of persistent cough illnesses in adolescents and adults result from *B pertussis* infection, a figure which might actually be an underestimate because of diverse clinical presentation in these age groups.

As mentioned, adolescents are an important source of infection and can be the source in up to 20% of cases. Thus, booster vaccination for this age group not only aims to increase protection for the individual, but also reduce transmission of the disease in the general population. Indeed, the introduction of a dTpa booster to adolescents aged 14–16 years in the Northwest Territory in Canada in 2001 led to a reduction in pertussis incidence throughout the whole population. Bearing in mind the relatively young demographics of this region, adolescents were thought to have been the primary reservoir of infection.

Health-economic analyses and mathematical simulations of the effect of vaccination suggest adolescent booster vaccination might be beneficial. For example, as part of a US analysis of many pertussis

![Figure 2: Incidence of pertussis infection in German states without (A) and with (B) preschool booster vaccinations](Reproduced with permission from Hellenbrand and colleagues.)
vaccination strategies, immunisation of adolescents (aged 10–19 years) was projected to be the most cost-effective approach. The study investigators established that in 10 years, this strategy might prevent 0.4–1.8 million adolescent cases of pertussis in the USA and save US$0.3–1.6 billion (direct and indirect costs).100

Timing of booster vaccination in adolescents is important. On the basis of the aforementioned findings, the COPE group propose that adolescents aged 10–17 years should receive a combined dTpa vaccine instead of dT, irrespective of complete primary vaccination schedule or type of previous pertussis booster vaccine. Adolescents aged 10–17 years who have a history of pertussis generally could receive a dTpa vaccine instead of dT, as such a history is an unreliable predictor of individual protection.

In the event of a pertussis outbreak, adolescents who received their previous pertussis immunisation more than 2 years earlier should receive dTpa.

Booster vaccination with dTpa has been well tolerated by adolescents who were immunised between 2 and 10 years after a previous diphtheria–tetanus-containing vaccine.102

Adolescents can be a hard-to-reach population and might have little perception of the outcomes of infectious disease and therefore a low interest in protection.101 Whenever feasible, integration of a dTpa vaccine strategy as part of the schooling system (ie, replacing the dT booster when appropriate) is likely to be one of the most promising methods of implementation. During an outbreak in a US high school, letters that were sent to parents emphasising the importance of vaccination for their children had a very small effect on the number of adolescents seeking vaccination from their doctor. A voluntary dTpa vaccination clinic was set up at the school, which resulted in an increase in coverage by about 31%.104

However, in locations where strong school health facilities are absent, other opportunities to provide vaccination should be considered, such as attendance at sports physicals or during health-care visits for other reasons.101 Implementation of dTpa boosters might be improved through coordination of the scheduling of vaccination to coincide with other immunisations, such as human papillomavirus vaccine.

Immunisation in adults

In view of successful vaccination programmes for infants and children, pertussis incidence has been increasing in older age groups. Epidemiological data from Canada show a more than 20-fold increase in incidence in adults since 1990, which might be attributable in large part to use of an inadequate pertussis vaccine in the 1980s.106 From the US surveillance data (1997–2003), 20–23% of pertussis cases were reported in adults (≥20 years), a proportion that seems to be gradually increasing.26,108 Reports from Europe have also highlighted the growing burden of pertussis in adult populations.26,108,109

Pertussis is a frequent cause of longlasting cough in adults, with studies suggesting that the disease underlies 10–32% of persistent coughing in adults.100,109,110 The Adult Pertussis Trial (APERT, sponsored by the US National Institutes of Health) was initiated in 1997 to investigate several characteristics of the disease in patients aged 15–65 years and the effects of acellular pertussis vaccination. 2781 individuals were randomly allocated to two groups: a control group who received hepatitis A vaccine and an immunisation group who received an acellular pertussis vaccine. During follow-up, prolonged cough illness was commonly reported (63% of patients per year), with pertussis underlying between 0.7% and 5.7% of episodes in controls dependent on the duration of cough.106 Overall incidence for this age group was 370 cases per 100 000 people per year, suggesting a million pertussis cases every year in the USA in people older than 15 years if this rate were applied to the total population.106 The investigators also suggested that there are about five patients who are asymptomatic or who have clinically insignificant infection for every classic case of clinical pertussis in adolescents and adults, a population which is a potential source of disease transmission.107 Vaccination reduced the risk for pertussis by 92%.106

From Markov modelling, a German study108 concluded that a dTpa vaccination programme for adults (aged 20–64 years) would be cost effective based on a disease incidence of 165 per 100 000 people per year and could even be cost-saving if the incidence were higher than 200 per 100 000 people per year. A US cost–benefit analysis concluded that although more expensive than adolescent boosting, decennial adult (≥20 years old) booster vaccination could prevent 0.9–4.7 million adult cases of disease and save $1.3–6.4 billion in the USA every 10 years.109

Timing of booster vaccination in adults should be considered on the basis of previous vaccination history. In view of the restricted period of immunity conferred by natural infection or immunisation, and assuming that both preschool and adolescent boosters have been established, the COPE group proposes that adults aged 18 years or older could benefit from a single dose of dTpa instead of dT for active booster vaccination, if they received their preceding dose of dT more than 10 years earlier irrespective of pertussis disease history. Although administration of a regular dTpa booster vaccine (eg, every 10 years) throughout adulthood could maintain pertussis immunity in this group, we recognise that a regular adult booster throughout life would pose a substantial challenge for many countries at the moment.

Intervals of less than 10 years since the last dT vaccination may be used to protect against pertussis. However, further epidemiological studies are mandatory to define the appropriate interval. In regions or situations where pertussis risk is increased, a single dose of dTpa at an interval of less than 10 years generally outweighs the risk for adverse reactions after
vaccination. Studies have shown that intervals of 18 months in adolescents\(^ {105} \) and as short as 4 weeks in adults\(^ {106} \) since a previous dT-containing vaccine are well tolerated with no significantly increased risk of adverse events.

In some European countries, booster vaccinations for health-care workers are recommended (table 1). Although vaccination of key health-care workers might be implemented as part of a cocooning strategy, more widespread targeting of health-care workers could be implemented in isolation or as a complementary strategy. The need for protection of health-care workers is supported by reports that outbreaks of pertussis in hospitals are common and these workers are usually the first affected.\(^ {29} \) Perhaps more importantly than the direct care of health-care workers, this group is often the source of infection for clusters of cases of disease occurring in patients in health-care settings.\(^ {29} \)

In addition to targeting of close family members of newborn babies as part of a cocooning strategy, opportunities to provide dTpa boosters with other vaccinations could be explored, such as individuals seeking travel vaccination or through occupational health visits, recipients of regular influenza immunisations, and in place of usual tetanus prophylaxis for wound management.\(^ {110} \)

### Turning proposals into practice

For the strategies discussed in this Review to be successfully implemented, national vaccination policy makers need to be convinced of the usefulness of present immunisation programmes and of the need to expand these programmes to improve control of pertussis. Education of the health-care community and increased public awareness of the existence and significance of pertussis beyond childhood, the contagious nature of the disease, and the potential risks for individuals and their children will also be key. Although availability of disease information in health-care settings (eg, leaflets and posters in doctors’ offices and hospitals) will be useful for people already within the health-care system, access to the media (newspapers, magazines, and internet advertising) will be needed to inform the outside community. Additionally, posters displayed in public places, such as the workplace, could serve as useful reminders for the general public.

Computerised record reminders that automatically highlight when individuals are due or overdue for vaccination may be useful aids to doctors, particularly when linked to reminder and recall strategies (eg, postcards, emails, and SMS messages). Such reminders would likely have the greatest effect when combined with improved availability of vaccine services to prompt increased uptake. Increased availability might include reduction of the distance between vaccination clinics and target vaccinees, increased or more convenient hours during which vaccination services are provided, and setting up drop-in clinics or express-lane vaccination services. In some countries (eg, Germany), provision of vaccine passports or cards for individuals to keep a record of their own vaccination status also enables them to monitor their situations. The availability of vaccines that are free at the point of delivery will also improve vaccination uptake.

Some of the activities mentioned here were employed for 2-5 years in the Netherlands to try to improve rates of influenza immunisation.\(^ {111} \) A coordinated collaborative nationwide programme of primary-care education and training, provision of patient information and reminder cards, employment of dedicated facilitators, and the introduction of supportive computer software served to significantly increase influenza vaccine uptake from 9% to 16% (increase of 78%; p<0.001).\(^ {111} \)

### Pertussis outbreaks

Management of pertussis outbreaks is labour and resource intensive and necessitates early diagnostic testing, aggressive antibiotic treatment and prophylaxis for high-risk contacts, accelerated infant vaccination, isolation of cases, and vaccination of potential contacts. As proposed in other sections of this Review, all potential contacts (eg, families or school and college students) in outbreak situations should be considered for booster vaccination. Intervals as short as 18 months in adolescents and even 1 month in adults since the last dT-containing vaccine can be considered in these patients to ensure protection for the individual and the community.

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**Table 4: Objectives of pertussis immunisation strategies**

<table>
<thead>
<tr>
<th>Primary objective</th>
<th>Secondary objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Universal adult</td>
<td>Reduce morbidity in adults; develop herd immunity</td>
</tr>
<tr>
<td>Cocoon</td>
<td>Reduce transmission to infants</td>
</tr>
<tr>
<td>Health-care workers</td>
<td>Reduce transmission to patients</td>
</tr>
<tr>
<td>Childcare workers</td>
<td>Reduce transmission to infants</td>
</tr>
<tr>
<td>Universal adolescent</td>
<td>Reduce morbidity in adolescents and adults; develop herd immunity</td>
</tr>
<tr>
<td>Preschool or school booster at 4–6 years of age</td>
<td>Reduce morbidity in 4–6 year olds; develop herd immunity</td>
</tr>
<tr>
<td>Reinforce the present infant strategy</td>
<td>Reduce morbidity in infants and toddlers; develop herd immunity</td>
</tr>
</tbody>
</table>

Adapted with permission from Forsyth and colleagues.\(^ {116} \) Although national vaccination policy makers can choose any one or more of the strategies listed, the Consensus on Pertussis Booster Vaccination in Europe (COPES) group recommend that a step-by-step approach be taken. For example, first preschool or school booster, then universal adolescent, cocoon, and finally universal adult strategies.
Conclusions
Neither natural infection nor vaccination provides lifelong protection against pertussis, and, despite the existence of childhood immunisation programmes, *B pertussis* continues to circulate in all developed countries. Although *B pertussis* infection in adolescents and adults is prevalent, mild or atypical symptoms in these groups contribute to misdiagnosis and under-reporting. Pertussis should therefore be considered in the differential diagnosis of cough illnesses lasting more than 1–2 weeks.

As with the rest of the world, policy makers in European countries need to consider regular pertussis booster vaccination in preschool children, adolescents, and adults to protect individuals and interrupt transmission of infection, which will also protect susceptible infants who are incompletely vaccinated or unvaccinated. These considerations are in line with both the Advisory Committee on Immunization Procedures recommendations for the USA and the recommendations from the Global Pertussis Initiative.

Although recommendations are a first step towards introduction of pertussis-booster vaccinations, in practice successful implementation in different age groups is challenging. For example, an assessment of compliance with immunisation recommendations for adolescents in Erlangen, Germany reported that about 40% of the sample of students were not immunised against pertussis.

To turn proposals into practice, the general public and health-care providers need to be trained or informed about pertussis. In Canada, for example, although adolescent pertussis booster vaccines are provided to students in school, continuation of medical education programmes for family doctors and paediatricians ensured that doctors were well informed and supportive. Education of public health nurses and information provided to the general public in the lay press were also essential parts of the education programme. Reminder systems (by telephone, mail, or electronic media) and an increased number of opportunities for individuals to be immunised (eg, in schools, emergency departments, obstetrics and gynaecology departments, travel clinics, and occupational health services, or introduction of longer doctor’s office hours) would also contribute to turn policy into practice.

Thus, the COPE group emphasises the need for pertussis booster vaccinations beyond childhood and, additionally, proposes implementation of a cocooning immunisation strategy to protect non-immune infants and replacement of dT boosters with dTpa for adolescents and adults in vaccination schedules across Europe. Table 4 provides a summary of objectives for immunisation strategies.

Contributors
All authors discussed and agreed upon the concept and objectives of the paper, contributed to the review and interpretation of the published work, and reviewed and approved all versions of the report. All authors contributed equally.

Conflicts of interest
EB has received honoraria and travel expenses from GlaxoSmithKline (GSK) Biologicals for Consensus on Pertussis Booster Vaccination in Europe (COPE) meetings and provided expert testimony for GSK Biologicals. NG has received travel expenses and been paid for consultancy for GSK Biologicals. UH been paid for consultancy and received honoraria from GSK Biologicals and Sanofi Pasteur MSD. JM has been paid for consultancy and received travel expenses from GSK Biologicals; JM’s institution has received payment from GSK Biologicals for research into a decennial administration of Boostrix vaccine in adults. JR has been paid for consultancy and received honoraria and speakers’ bureau fees from GSK Biologicals. AET has received travel expenses from Wyeth and GSK and for trials on conjugated pneumococcal polysaccharide and rotavirus vaccines. PVD is the principal investigator for clinical trials done on behalf of the University of Antwerp, for which the university obtains research grants from vaccine manufacturers; PVD’s fees for presentations on vaccines are paid directly to an educational fund held by the University of Antwerp. FZ received travel expenses from GSK Biologicals, Novartis, and Sanofi Pasteur. The University Medical Center Mainz received payments/honoraria from GSK Biologicals, Novartis, and Sanofi Pasteur for lectures and expert consultancy provided by FZ.

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References


Black S, Friedland LR, Schuind A, Howe B. Immunogenicity and safety of a combined DTaP-IPV vaccine compared with separate DTaP and IPV vaccines when administered as pre-school booster doses with a second dose of MMR vaccine to healthy children aged 4–6 years. Vaccine 2006; 24: 6163–71.


