Recent developments in pertussis

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Pertussis causes nearly 300 000 deaths in children every year. Most deaths take place in developing countries, but the infection remains a priority everywhere. Pertussis vaccination protects infants and children against death and admission to hospital, but breakthrough disease in vaccinated people can happen. In high-mortality countries, the challenge is to improve timeliness and coverage of childhood vaccination and surveillance. In regions with low mortality and highest coverage, pertussis is frequently the least well-controlled disease in childhood vaccination programmes. Some countries have reported a rise in pertussis in adolescents, adults, and pre-vaccination infants, but how much these changes are real or a result of improved recognition and surveillance remains uncertain. In response, several countries have introduced adolescent and adult acellular pertussis vaccine boosters. The effect so far is unknown; assessment is impeded by poor data. Uncertainties still persist about key variables needed to model and design vaccination programmes, such as risk of transmission from adults and adolescents to infants. New vaccination strategies under investigation include vaccination of neonates, family members, and pregnant women.

Pertussis is a fascinating, important, and challenging disease for doctors, microbiologists, epidemiologists, and policymakers in every country. Despite being preventable by vaccination for several decades, pertussis remains one of the top ten causes of death worldwide in childhood, mainly in unvaccinated children.[1,2] Experts still debate basic characteristics of the disease. Why does the cough last so long? How does the duration of immunity after infection compare with that after vaccination? To what extent does herd immunity exist? The optimum strategies for improving control of pertussis remain uncertain. Every country has a different vaccination programme history. Even in countries with strong vaccination programmes the infection continues to kill young children, doctors still miss the diagnosis, and robust data for disease incidence remain sparse. In this Seminar we summarise recent developments that enhance our understanding of pertussis diagnosis, management, prevention, and control, and we identify those key points about which questions still remain.

Clinical features of pertussis

Pertussis (whooping cough) is an infectious respiratory disease caused by the bacterium *Bordetella pertussis*, an exclusively human pathogen recorded worldwide. The differential diagnosis includes a wide range of respiratory pathogens, such as *Bordetella parapertussis* and respiratory syncytial virus infection.[3]

Search strategy and selection criteria

In 2005, a literature review was undertaken using MEDLINE complemented by a collection provided by WHO Geneva originally compiled by Artur Galazka and then extended to include articles held in WHO regional databases. MEDLINE searches of articles used the MeSH terms "pertussis complications", "epidemiology", "mortality", "prevention and control", and "transmission" to identify articles published since 1966. Papers were prioritised to meet the space constraints of the Seminar.

Pertussis is very infectious with high secondary attack rates in households.[4] Published incubation periods range between 5 and 21 days, with 7 days being most common, and rarely lasting beyond 10 days.[5–7] These incubation periods usually take the onset of cough as being the onset of disease, although the cough is usually preceded by a non-specific prodromal coryzal illness, which can be easily missed. The infectious period is usually taken as the onset of this catarrhal prodrome to 3 weeks after onset of illness.

The cough that follows the prodrome is characteristic and is most typically paroxysmal followed by a whoop or vomiting, or both. Clinical severity varies widely, with mild cases seen particularly in older children, adults, and vaccinated individuals (panel 1).[4] In recent times asymptomatic infection, but not carriage, has been recognised.[8,9] Infants might not develop paroxysms or a whoop and present only with apnoea or sudden death.

Complications of pertussis usually happen in childhood and include pneumonia, failure to thrive from post-tussive vomiting, seizures, encephalopathy, cerebral hypoxia leading to brain damage, secondary bacterial infection, pulmonary hypertension, sub-

Panel 1: What affects the clinical presentation of pertussis?

Age
Adults and older children are less likely to have typical symptoms—eg, simple cough
Very young infants might present atypically—eg, with apnoea alone—and not cough

Previous infection
Subsequent infections are milder

Previous vaccination

Time since previous vaccination or infection
Longer time, increased severity of infection

Co-infection

conjunctival haemorrhage, and rectal prolapse. Nearly all deaths take place in the first 6 months of life,[10,11] with substantial underascertainment.[10,12]

Evidence is gathering on the occurrence of adult pertussis.[13,14] Although adolescents, adults, and even elderly people can present with typical disease, more frequently it is a simple prolonged cough.[11] In 13–20% of adults with prolonged cough, pertussis is the cause,[15] and 21–86% present with typical symptoms[16–22] frequently with coughing for 7–8 weeks.[18,23] Complications in adults include urinary incontinence,[21] admission to hospital,[24] hearing loss, inguinal hernia, pneumothorax, aspiration, cracked ribs, carotid artery dissection, pneumonia,[16] and death (rarely).[25]

The disease remains underdiagnosed by both paediatricians and family doctors, so increasing awareness and reporting of pertussis is a priority (panel 2). Early diagnosis can lead to more effective treatment and control measures, such as prophylaxis for contacts at risk, thus preventing further cases and avoiding inappropriate investigations. Prompt reporting allows public-health authorities to know if and why vaccination programmes might not be working and action can be taken accordingly.

Microbiology

B pertussis is a small gram-negative coccobacillus, strictly aerobic, and fastidious, needing special media (such as charcoal blood agar with cefalexin) for its isolation. The bacterium produces a range of adhesins, fimbriae, and toxins. Some are associated with adhesion and colonisation, including filamentous haemagglutinin, pertactin, and components of pertussis toxin, and some are implicated in the pathogenesis of clinical pertussis, including other components of pertussis toxin, an adenylate cyclase toxin, dermatonecrotic toxin, tracheal cytotoxin, and pertussis lipo-oligosaccharide (figure 1). The entire genome of *B pertussis* has been sequenced, as have those of *B parapertussis* and *Bordetella bronchiseptica*.[26] The pathogenesis is much more complex than some other bacterial pathogens because of the range of different factors implicated. Although the role and regulation of virulence factors has been delineated in some detail, there is no sole factor that can be inhibited to prevent disease (hence the most effective vaccines contain more than one or two antigens).

Recent developments in diagnostic methods

From a worldwide perspective, the challenge is for all countries to be able to provide a basic laboratory diagnostic service because many developing countries have none at all.[27] In developed countries, laboratory diagnostic methods for pertussis have been evolving from culture and serology to antigen detection and PCR. Every alternative has its strengths and limitations.[28,29]

Panel 2: Clinical management algorithm

Clinical suspicion of pertussis

Suspect pertussis in patients with a cough illness lasting at least 2 weeks with one of:

- paroxysms of coughing
- inspiratory "whoop"
- post-tussive vomiting

Suspect the diagnosis in anyone with a pertussis-compatible illness also linked in time and place to another confirmed case

Note that young infants can present with apnoea or sudden death alone

Note that older children, adults, and vaccinated individuals might have a simple cough only

Laboratory investigation

If within 3 weeks of onset then take nasopharyngeal aspirate for culture and PCR—pernasal swabs are an alternative

Transport to the laboratory immediately

If more than 2 weeks from onset consider taking serum for pertussis toxin IgG

If strongly suspect the diagnosis, or on laboratory confirmation

- Treat the patient awaiting diagnosis
- Consider infection control—isolate case if necessary
- Report the case to relevant authorities
- Offer prophylaxis to vulnerable contacts

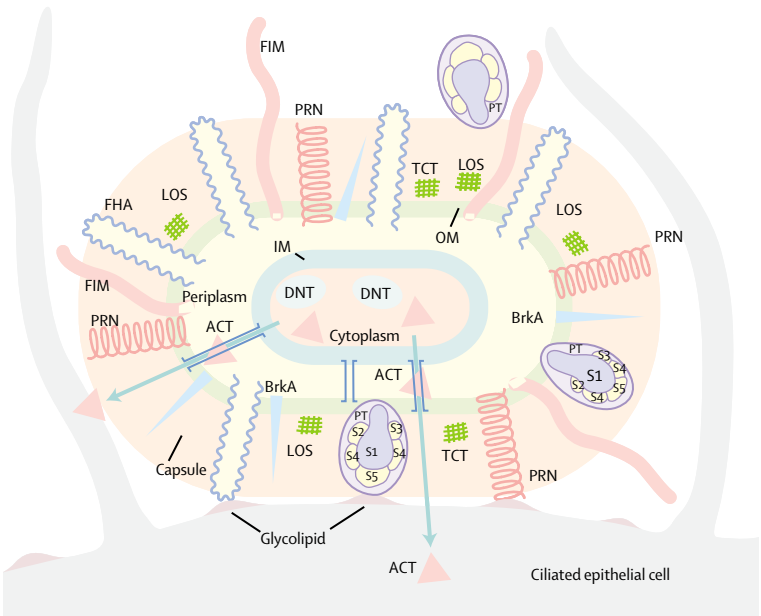
Culture

Culture has been taken as the gold standard diagnostic method although, despite being highly specific, it is an insensitive technique. Sensitivity is lower if the specimen is taken later in the illness (falling to 0% by 3 weeks after onset), for specimens other than nasopharyngeal aspirate, if there are delays in transporting the specimen, in older and vaccinated individuals, and in those who have received antibiotics (panel 3). Even when patients have been coughing for fewer than 21 days, sensitivity of culture can be as low as 15–45%.[30–32]

The strength of culture lies in allowing typing and antibiotic sensitivity testing (although resistance is rare).[33,34] Typing has been applied to understand whether and why pertussis might be re-emerging and to track transmission in families.[35] Standard epidemiological typing of *B pertussis* has been proposed on the basis of serotyping, pulse-field gel electrophoresis, and gene typing.[36,37]

PCR

PCR-based diagnostic methods have been developed to improve diagnostic sensitivity,[38,39] but every protocol needs validation to avoid false-positive results.[40] Similar to culture, PCR is less likely to be positive as the duration of the illness progresses but is affected less by antibiotic treatment. Further developments in rapidity, simplicity, and standardisation are continuing.[38] A commercial test



Antigen	Function
Agglutinogens including fimbriae (FIM)	Attachment to ciliated respiratory epithelium possibly important for type-specific immunity
Filamentous haemagglutinin (FHA)	Adhesion and immunomodulation
Pertactin (PRN)	Adhesion. Important immunogen
Pertussis toxin (PT)	Attachment of *B pertussis* to ciliated respiratory cells. Important immunogen Activates cyclic adenosine phosphate (cAMP), histamine sensitising factor (HSF), lymphocytosis promoting factor (LPF), islet-activating protein (IAP), interferes with leucocyte function, haemolytic
Adenylate cyclase toxin (ACT)	Activates cAMP, interferes with leucocyte function, haemolytic
Dermonecrotic toxin (DNT) or heat-labile toxin	Unknown role in vivo. Dermal necrosis and vasoconstriction in vitro
Tracheal cytotoxin (TCT)	Ciliostasis, inhibition of DNA synthesis, kills ciliated epithelial cells
Lipooligosaccharide (LOS)	Causes fever
BrkA (*Bordetella* resistance to killing genetic locus, frame A)	Outer membrane protein that mediates adherence and resists complement

***Figure 1:* *Bordetella pertussis* antigens**
IM=inner membrane. OM=outer membrane. S1–5=subunits 1–5.

approved by the US Food and Drug Administration is not yet available, so PCR sensitivity and specificity might vary from laboratory to laboratory. A European assessment has shown that false positivity is not an issue in many laboratories, but the target chosen is essential for species specificity.[41]

Different targets have been used for PCR, including insertion sequences, the pertussis toxin promoter region *ptxA*, the adenylate cyclase gene, and the porin gene, with sensitivities ranging from 73% to 100%.[29,42] The specificity of PCR is thought to approach 100%, but this is difficult to evaluate against the standard method, culture, because PCR has much higher sensitivity than

***Panel 3:* What reduces the sensitivity of culture?**

Nasopharyngeal aspirate >pernasal swab >throat swab
Incorrect method of taking swab of respiratory mucosa (eg, sweep of anterior nares only)
Incorrect swabs (cotton and rayon are inhibitory)
Longer duration of illness (to 0% at >3 weeks) after onset
Delayed transport of specimen to laboratory
Drying of the specimen
Transport in incorrect transport medium (some are inhibitory)
Wrong culture media
Laboratory contamination

culture.[27] However, assessing a new test that has greater sensitivity than culture is difficult.[27] Cross-reaction with *B parapertussis* is avoided because this bacterium does not produce pertussis toxin. False-positives might be produced by *Bordetella holmesii* and *B bronchoseptica* using the insertion sequence *IS481* target, because they possess IS481-like sequences.[43–45]

Serology

Serology has proved especially useful for later diagnosis of prolonged cough in older children and adults when results of both PCR and culture are negative.[42,46–48] Antibodies to several antigens have been investigated for diagnosis, including IgG or IgA antibodies to pertussis toxin[49] and to filamentous haemagglutinin, fimbriae, and pertactin.[50–53] Pertussis toxin antibodies are specific for *B pertussis*, but antibodies to filamentous haemagglutinin, pertactin, fimbriae, and whole sonicated organism might be raised after infection with other *Bordetella* sp including *B parapertussis*.[54] Cross-reactions can happen with filamentous haemagglutinin of non-encapsulated *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.[55] Anti-pertussis toxin IgA and antibodies to fimbriae and pertactin do not seem to add greatly to the diagnosis compared with anti-pertussis toxin IgG alone.[29] Combining antigens improves sensitivity but is impracticable and expensive for routine diagnostic services.[9]

Serological diagnosis on the basis of anti-pertussis toxin IgG or IgA has been used routinely for diagnosis in several countries including Australia,[56] Austria, Finland, France, Netherlands, Norway, and the USA.[50,51,57] A single high titre of anti-pertussis toxin IgG has good predictive value for current infection, with sensitivity of 76% and specificity of 99% for diagnosis of acute pertussis.[49] Concentrations of anti-pertussis toxin IgG fall below the defined cut-off on average about 4·5 months from infection, and in most patients (82%) within 1 year.

Diagnostic algorithms

Different countries have developed a range of laboratory diagnostic algorithms, but in general, culture and PCR

are recommended if specimens can be obtained early in the illness and serology if specimens are obtained later on. Thus, PCR is generally most useful for infants, who present acutely unwell, and serology is preferred for older children and adults, who tend to present after a prolonged coughing illness. In the USA, investigation by culture and PCR is recommended during the infectious period, 3 weeks from onset of cough or 4 weeks from onset of symptoms.[11]

Treatment and prophylaxis

Treatment

Supportive treatment is most important for infants. For optimum clinical effectiveness, antibiotic treatment should be given rapidly: it also shortens the infectious period.[33] There is probably no effect on outcome if started more than 1 week after onset of illness. Erythromycin is the traditional treatment, but the newer macrolides azithromycin and clarithromycin have similar effectiveness with fewer side-effects.[58,59] 7 days of treatment with erythromycin have been shown to be as effective as previous regimens of 14 days of erythromycin.[60] If macrolide antibiotics are contraindicated, trimethoprim-sulfamethoxazole is an alternative.[11] Clearance of the organism is especially important for those in contact with high-risk individuals, such as infants, health-care workers, and pregnant women about to give birth.[61]

Prophylaxis

Macrolide antimicrobials are also recommended for prophylaxis.[62–64] Protection by any antimicrobial is limited, however, and potential side-effects are important, so their use should be restricted to situations in which benefit is likely to be greatest—ie, within 3 weeks of onset of the index case and only if there is a vulnerable contact in those most closely exposed.

Vaccination and immunity

Whole-cell and acellular pertussis vaccines

Whole-cell pertussis vaccines were developed in the 1940s and have been used worldwide for many years, having been part of the WHO Expanded Program of Immunization since its launch in 1974. Whole-cell pertussis vaccine is a suspension of killed *B pertussis* organisms. Safety of whole-cell vaccines has been reviewed in detail, and of a range of adverse events considered, evidence suggests a causal relation only for anaphylaxis, prolonged or inconsolable crying, and febrile seizures.[65] For other events, including sudden infant death syndrome, data do not indicate any causal link, and for some disorders the evidence is insufficient to draw a definitive conclusion. Concerns about safety led to the development of acellular pertussis vaccines in the 1970s. Acellular vaccines consist of up to five specific *B pertussis* antigens, including pertussis toxin, filamentous haemagglutinin, pertactin, and two fimbrial antigens (FIM 2 and FIM 3). Although clinical trials have reported lower rates of adverse events than whole-cell vaccines, large and painless local reactions (measuring >50 mm and affecting whole limbs), with a clinical appearance similar to cellulitis, have been seen in 1–2% of booster recipients, but without medical sequelae.[66,67] The probability of a reaction seems to be highest in recipients of boosters in whom acellular vaccines were used for priming.[68]

Different whole-cell and acellular pertussis vaccines give very diverse antibody responses, which are essential to distinguish the effect of infection and vaccination.[51,69] Some pertussis vaccines (either whole-cell or acellular) induce a much lower pertussis toxin response than acute infection, whereas others might provoke a much higher pertussis toxin response, which can be hard to differentiate from infection.[70]

Comparison of natural and vaccine-induced immunity

Our understanding of duration of immunity after natural infection and vaccination and the degree to which these are affected by exposure to circulating *Bordetella* sp is incomplete.[71] The relation between antibody and protection is not straightforward, with no particular serological correlate of protection,[72,73] although antibodies to some *B pertussis* antigens seem more strongly linked than others.[9] Little is known about the role of cell-mediated immunity, but it is essential for recovery from natural infection and in long-term protective immunity.[74]

Neonates are protected from many infectious diseases by maternal antibodies. For pertussis, less maternal protection is provided than for other diseases—eg, measles. Some researchers suggest some protection exists during the first month of life,[75] but by 4 months most infants have no detectable maternal antibody.[76]

Naturally acquired and vaccine-induced immunity decline with time, with debate about which declines fastest.[77,78] The relation is confounded by boosting from natural infection.[23,79–82] In a review, duration of immunity post-infection ranged from 7 to 20 years and post-vaccination from 4 to 12 years.[71]

Measuring the effectiveness of pertussis vaccines is not straightforward[83] and many factors are important, such as case definition, age at vaccination, the setting of exposure, time since vaccination, and vaccine characteristics. Duration of protection after vaccination also varies between vaccine type, schedule, level of exposure, and age at first vaccination.[83] In general, any vaccine type has good effectiveness, but whole-cell vaccines tend to have higher short and longer-term potency than one or two component acellular vaccines and similar effectiveness to the three-component or five-component acellular vaccines. Some whole-cell vaccines have had poor effectiveness (eg, Connaught whole-cell vaccine).[84–86] The Evans whole-cell pertussis vaccine used in the UK until 1999 had high effectiveness of about 85%.[87–89] In recent years, many children have received a mixture of different types as new vaccines have become

available; children who are primed with a whole-cell vaccine and later given an acellular booster seem to have the best levels of protection.[90] Trial evidence of an acellular pertussis vaccine booster for adolescents and adults has suggested direct vaccine protection of up to 92%.[91]

Vaccine effectiveness also varies depending on the case definition. In the first year after vaccination, vaccine effectiveness of a primary course is estimated as 100% against fatal or severe disease, 90% against typical disease, and only 70% against mild disease; one dose of vaccine is probably effective protection against death from pertussis.[83,92–94] Immunity possibly wanes after vaccination from being fully protected through different levels—eg, susceptible only to mild disease, typical, and then severe disease. Similarly, severity of reinfection increases with time since previous infection.[95] Thus, high coverage, which reduces circulation of the organism, reduces exposure and natural boosting of immunity, delays time to reinfection (or exposure), and paradoxically might heighten the severity of reinfection.[96]

Vaccination recommendations and schedules

Most nations use whole-cell vaccines because they are cheap, effective, and easy to produce. Most developed countries have switched to acellular vaccines. Most countries have a three-dose primary immunisation series starting at 6 weeks to 3 months, usually completed by 6 months, which forms part of the WHO Expanded Program of Immunization. Many schedules include a toddler booster, and many a fourth or fifth dose at 4–6 years of age. Current vaccination strategies developed in response to perceived changes in the epidemiology of pertussis are summarised below.

Epidemiology and effect of preventive strategies

Routine surveillance

Surveillance of pertussis is a challenge because the clinical range is wide, all ages can be affected, and laboratory confirmation is not straightforward. Data from different countries are difficult to compare because surveillance systems vary greatly: case definitions, diagnostic methods, clinical and reporting practice, and public-health law all differ.[97] Surveillance of pertussis in most countries relies on statutory clinical notifications and laboratory reports.[98] Both are recognised to underestimate the level of pertussis greatly and to vary in sensitivity and specificity of reporting between epidemic and non-epidemic periods, between vaccinated and unvaccinated individuals, and between younger and older children or adults.[99–101]

Clinical notifications are not sensitive for infection with *B pertussis*, particularly in older children and adults who frequently present with atypical symptoms (eg, cough alone) and rarely with paroxysms, vomiting, or whoop. Notifications are likely to greatly underascertain people with mild infections, including the very young, vaccinated individuals,[99] older children, and adults. Nevertheless, a clinical case definition of 14 or more days cough can have a sensitivity as high as 84–92% (better than culture) and specificity of 63–90% during periods when pertussis is prevalent.[99,102]

Laboratory reports are highly specific but generally less sensitive than clinical notifications. Infants are over-represented in reports because they are more likely to be admitted to hospital and appropriately investigated.[99]

The case definition applied in a surveillance system will have a strong effect on the sensitivity and specificity of the system. Various case definitions for pertussis exist that need to be adapted for different circumstances. WHO's clinical trials case definition[27] is too specific and not sensitive enough for surveillance purposes. Definitions suitable for use in outbreaks might not be specific enough at other times.[103] WHO, USA Centers for Disease Control, and the European Union now have similar surveillance case definitions.[27,104,105]

Sero-epidemiology

Population sero-surveys using high titres of anti-pertussis toxin IgG as a marker of current infection have shown widespread distribution in the general population. Infection is substantially more likely in adolescents and adults in high-coverage countries (≥90%, Finland, Netherlands, France, eastern Germany), but it is more likely in children than adolescents or adults in lowest coverage countries (<90%, Italy, western Germany, the UK).[51] This corresponds to recent observations made from pertussis surveillance in high coverage countries. This rise in the mean age at infection when coverage is high could be related to interruption in transmission in youngest age-groups, waning immunity in vaccinated cohorts, or both. However, the public-health importance of high titres of anti-pertussis toxin antibody in population sero-surveys both clinically and in terms of transmission remains uncertain.

Epidemic cycles, age at infection, and secular trends

Pertussis shows annual seasonal peaks and a 2–5 yearly epidemic cycle. These cycles of pertussis have been seen in many countries.[106] Before the vaccination era, the infection was typically recognised and reported in children younger than 10 years old, usually 3–6 years of age.[5] Although previous analyses have been conflicting, work has suggested widespread pertussis vaccination does lead to both a rise in the inter-epidemic period and the mean age of infection, which is congruent with a reduction in pertussis transmission after vaccination.[106] Pertussis has seasonality but it is not consistent in time and place.[107–110]

Herd immunity

Protection of infants during the first few months of life before vaccination has started or is completed depends crucially on whether indirect protection is provided by

herd immunity. There has been debate about whether pertussis vaccination induces herd immunity to the extent of other childhood vaccines because epidemic cycles continue despite vaccination.[83,101,111] Is the vaccine more effective at protecting the individual from severe outcome of infection (eg, death) rather than preventing infection (and thus transmission)?

Evidence suggests pertussis vaccination does reduce transmission and provides indirect protection.[112] The incidence of infection has fallen in infants younger than 3 months old (who can only be protected indirectly), indicating that either vaccination or some other factor has reduced transmission.[101] In Denmark, the level of indirect protection of infants with 90% vaccination coverage was estimated at more than 87%.[113] In Senegal, pertussis vaccine effectiveness in preventing infection in people exposed to an infected vaccinated individual was 86%, close to the level of direct protection derived by vaccination.[114]

Interpretation of present trends

Pertussis has not been eliminated from any country despite decades of high vaccination coverage. A resurgence of the disease has been reported in some high-coverage countries in adolescents and pre-vaccination infants, including the Netherlands, Belgium, Spain, Germany, France, Australia, Canada, and the USA.[84,108,109] Rates reported in studies of adolescents and adults have risen and reached incidences of 300 to more than 500 per 100 000 person-years in several different countries.[115] Evidence shows adults play an important part in passing infection to young infants,[116,117] sometimes with fatal consequences.[118] An increase in the number of deaths from pertussis in young infants has been reported,[109] although case fatality has remained fairly constant.[108]

Is pertussis incidence really rising in adults and infants in countries with high coverage or is the increase attributable to enhanced ascertainment? Improvements in laboratory methods leading to better surveillance probably partly account for the noted rise—particularly in adults and adolescents.[119] For example, in the USA, Massachusetts has reported more pertussis than many other states because of better surveillance.

In countries where a resurgence of pertussis has been validated, three reasons have been proposed: vaccine failure, changes in the organism, and the effect of the vaccination programme on dynamics of infection. Rises in Canada have been linked to use of a poorly effective vaccine.[84] Netherlands had a large resurgence of pertussis in 1996, which has been attributed to a change in the circulating organism.[120] Polymorphisms in the genes coding for pertactin and pertussis toxin were reported as evidence for vaccine-driven evolution of circulating strains leading to a fall in vaccine effectiveness.[120–122] Microbiologists in other countries have attempted to replicate the studies undertaken in Netherlands and have also found evidence of emergence of non-vaccine variants of pertactin and pertussis toxin,[123,124,37] but not accompanied by any changes in vaccine effectiveness in countries besides Netherlands,[125–129] suggesting the role of an additional vaccine-related factor. Netherlands has now switched from using a domestically produced whole-cell vaccine to acellular pertussis vaccine.

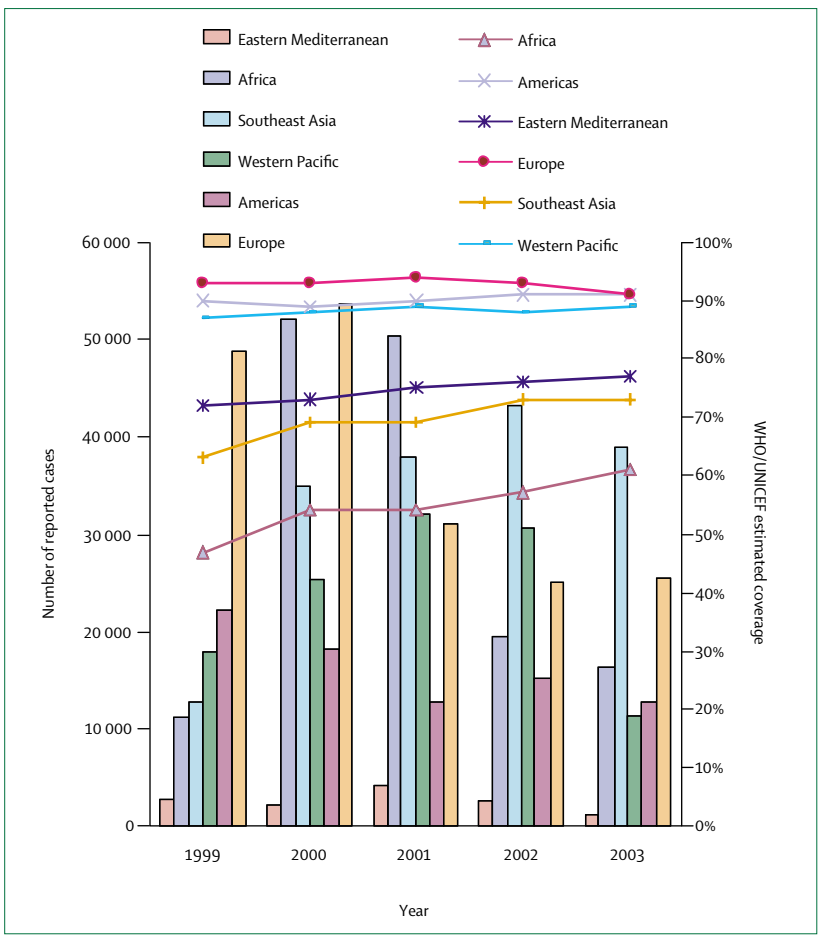


Figure 2: **Number of reported cases of pertussis and WHO/UNICEF estimated pertussis vaccination coverage in children less than 1 year old by WHO region, 1999–2003**

With respect to the effect of vaccination on the dynamics of infection, in general, countries with high coverage have a greater proportion of adolescent and adult cases than do those with lower coverage.[24,51,110,130] Although countries with strong vaccination programmes frequently have better surveillance and are perhaps most likely to detect cases in adolescents and adults, there is also evidence of a true increase—due in particular to waning vaccine-derived immunity. Secondary attack rates might be used as a proxy for the proportion of susceptible individuals. Studies confirm high rates of susceptibility with severity of infection correlating with time since vaccination.[95] Sources of infection for infants include mothers[8,116,119] and health-care workers.[131] By contrast, adolescents tend to be infected by schoolfriends.[13] The

role of these older age-groups in transmitting infection to pre-vaccination infants is being quantified.[132,133]

The epidemiology of pertussis in high and medium mortality countries is poorly described.[2] WHO estimated in 2002 that the number of deaths due to pertussis—all in children younger than 5 years of age—was 294 000.

Panel 4: Pertussis vaccination strategies proposed by the Global Pertussis Initiative

Universal adult immunisation
Selective immunisation of mothers and close family contacts of neonates
Health-care worker vaccination
Child-care worker vaccination
Adolescent vaccination
Pre-school booster 4–6 years
Re-enforcement and improvement of current infant and toddler strategies

Panel 5: Research and development priorities (adapted from 169 and 142)

Developing countries
- Burden of disease: mortality, morbidity
- Evaluating programme impact
- Sustainable cost-effective laboratory methods and algorithms
- Sustainable integrated surveillance
- Programme optimisation of schedule, coverage, and timely vaccination

Natural history in high coverage areas
- Herd immunity, transmissibility of infection in different age groups and with different severity of infection
- Define the full range of infectious and clinical disease including deaths from pertussis—eg, sudden unexplained deaths in infancy
- Effect of unreported cases, undiagnosed cases, and misdiagnosed cases
- Role of subclinical infection in shaping dynamics of infection
- Phylogenetics of *Bordetella*: How do different strains of the *Bordetella* complex interact directly or through immunity?
- Duration of immunity after infection and vaccination

Older age groups
- Reservoirs of infection and sources of infection for older age groups
- Effect of adolescent and adult boosters on infant disease
- Safety and effectiveness of vaccination in non-paediatric populations

Surveillance development
- Determine under-reporting extent by age and country
- Improve case ascertainment for surveillance
- Extend application of sero-epidemiology

Modelling and economic assessment
- Country and age-specific costs per case
- Epidemiology and costs of infections in special populations such as child-care workers
- Health utilities
- Modelling effectiveness of alternative intervention strategies with well parameterised models
- Cost-effectiveness of alternative vaccination strategies

Under-reporting is widespread. In 2004, 236 844 cases were reported to WHO, which is fewer than the number of estimated deaths in 2002 (figure 2). Worldwide coverage of the third dose of diphtheria toxoid, tetanus toxoid, and pertussis vaccine in 2004 was 78%, leaving 27 million children unprotected, of whom 75% were in sub-Saharan Africa and south Asia.[134]

Modelling and health economics

Mathematical models have been developed to try to assess the optimum approach to controlling pertussis.[77,135,136] These models have been limited because of uncertainty about factors, such as the effect of vaccination on transmission of *B pertussis* at different ages,[81,135,137] and patterns of mixing of different age-groups.[137] Various assumptions and estimates have been made, variation in any of which changes the findings from one analysis to another. Effectiveness of acellular pertussis vaccines has been estimated to be greater or less than that of whole-cell vaccines,[138] coverage has been assumed to have been and to remain stable at 95% for most analyses, secondary attack rates have been estimated at 12%, and all vaccination is assumed to be given on time.[139]

Direct costs[140] and hospital admission rates vary greatly by country. Few studies have measured indirect costs. The costs to society in the USA are dominated by non-health-care elements, including school loss and lost working days.[141]

Despite these uncertainties, many alternative interventions have been investigated. In Canada, a diphtheria, tetanus, and acellular pertussis booster at 12 years has been deemed cost beneficial.[142] By contrast, an Australian analysis showed vaccination of baby and parents at birth the most cost-effective approach (if an immunogenic vaccine for neonates existed).[143] Uncertainty about variables limited the ability to assess seven different adult and adolescent booster strategies in a study in the USA.[144]

Future vaccination strategies

In summary, designing intervention strategies for pertussis is limited by data quality. To be prudent, any schedule changes should account for the full range of scenarios, including the possibility that mass immunisation programmes could increase disease burden.

Two collaborations have raised the languishing profile of pertussis, calling for the introduction of adolescent and adult boosters.[145,146] Unfortunately, vaccine manufacturers have funded both, with obvious potential for conflict of interest. Enthusiasm for a worldwide resurgence has led some members of the collaboration to wrongly cite a rise in pertussis incidence in the UK,[147] for which there is not good evidence as yet.

Several strategies have been proposed by the Global Pertussis Initiative (panel 4).[148] Not one strategy is likely

to be appropriate to all.[149] In view of concerns about possible transmission from adolescents and adults to young children, several countries have recommended acellular booster doses for adolescents (including Australia, Austria, France, Germany, the USA, Canada) and some for adults (the USA, Australia, Austria). The effect of adolescent and adult boosters depends on the duration of vaccine-derived immunity and the level of indirect protection (to infants) generated. Both of these are surrounded with uncertainties, and there are practical challenges in achieving good coverage in adolescents and adults. Occupational vaccination for obstetric, paediatric, midwifery, laboratory staff, and child-care workers might be feasible, to protect staff, their patients and clients, and this strategy should be considered.[150]

Conclusions

Pertussis is a substantial health burden worldwide, and for many developing countries the challenge is simple—to achieve high vaccination coverage of timely immunisation for infants. Public-health authorities could do much to improve the quality of routine information used to assess changes to vaccination programmes, such as adolescent and adult boosters. All countries should apply standardised case definitions for surveillance and outbreak investigation, and make better use of laboratory diagnostic methods in all age-groups, including validated PCR and single high titre pertussis toxin IgG. For low-mortality countries, areas needing further research and development are many (panel 5). Although doctors, mathematical modellers, epidemiologists, researchers, and policymakers have made considerable progress in recent years in improving our understanding of pertussis, controlling this infection continues to present us with a complex and fascinating challenge.

Conflict of interest statement

We declare that we have no conflict of interest. The corresponding author had final responsibility for the decision to submit for publication.

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