

## **WHO Position Paper on Pertussis Vaccines: Selected references**

The following list includes some of the references that were consulted during preparation of the most recent WHO position paper on Pertussis Vaccines (Wkly Epidemiol Record 2005; 4 (28 Jan) 31-39. This position paper replaced the previous paper on this topic (WER 1999; 18 (7 May) 137-143).

Whereas most of the background information and policy statements remain the same in the two position papers, the 2005 paper emphasises developments during the period 1999-2005 especially in the fields of

- Epidemiology of pertussis
- Vaccine efficacy, herd effects and duration of protection
- Vaccine policy issues, including booster immunizations
- Other issues related to pertussis vaccination

## **Epidemiology of pertussis**

**Crowcroft NS, Stein C, Duclos P, Birmingham M. How best to estimate the global burden of pertussis? Lancet Infect Dis. 2003 Jul;3(7):413-8.**

*In most countries, pertussis surveillance is inadequate for accurately estimating numbers of cases or deaths. Good estimates are needed to help set priorities for vaccination programmes. We aimed to develop a simple, reliable, and explicit method for estimating pertussis cases and deaths for children under 15 years to calculate the global disease burden in 1999. We estimated the proportion of susceptible children becoming infected in countries with poor vaccination coverage (<70%) in 1999 at 30% by 1 year, 80% by 5 years, and 100% by 15 years of age and for countries with good coverage (> or =70%) at 10% by 1 year, 60% by 5 years, and 100% by 15 years. Vaccine efficacy was estimated at 80% for preventing infection and 95% for preventing deaths. We used UN population estimates and vaccination coverage reported to WHO (adjusted for specific survey data if available). Case fatality ratios for countries with high and low child mortality were derived from published and unpublished work. For some countries with good vital events registration we used reported deaths adjusted for underascertainment. In 1999 there were an estimated 48.5 million pertussis cases in children worldwide. Deaths from pertussis were estimated at 390000 and at 295000 after adjustment for local data sources. Based on this approach, disability-adjusted life years from pertussis (12.7 million) in 2000 exceeded those of other preventable diseases such as lung cancer (11.4 million) and meningitis (5.8 million). This simple approach yields estimates that can be used for setting vaccination programme priorities. Better data are needed on the public health*

*importance of pertussis in high mortality countries, the benefits of incomplete vaccination, and the harm from delayed vaccination.*

**Juretzko P, Fabian-Marx T, Haastert B, Giani G, von Kries R, Wirsing von Konig CH. Pertussis in Germany: regional differences in management and vaccination status of hospitalized cases. Epidemiol Infect. 2001 Aug;127(1):63-71.**

*The incidence of pertussis requiring hospitalization in children younger than 16 years was estimated by the use of an active surveillance-system. Of special interest were differences between West and East Germany following different vaccination strategies before reunification. In 1997 and 1998, 754 pertussis cases required a total of 11,151 hospital inpatient days. The incidence of hospitalized pertussis was 2.68/100,000 person years and this was significantly higher in East than in West Germany. In East Germany an unusually high percentage of hospitalized cases was found in children aged 6-15 years (45% versus 13% in West Germany). The difference between the regions may be due either to a different perception of the disease or to an increased immunity induced by prior disease or vaccination. In East Germany, pertussis was rare until reunification but it has increased significantly since then. Older children may thus represent a population at risk of pertussis having not had previous exposure to pertussis antigens.*

**Preziosi MP, Yam A, Wassilak SG, Chabirand L, Simaga A, Ndiaye M, Dia M, Dabis F, Simondon F. Epidemiology of pertussis in a West African community before and after introduction of a widespread vaccination program. Am J Epidemiol. 2002 May 15;155(10):891-6.**

*The control of pertussis remains a worldwide concern. Little has been documented about its epidemiology in Africa. The authors have studied pertussis in a prospective cohort of children in a rural West African community over a 13-year period comprising time before and after introduction of a vaccination program. Children under age 15 years who were residents of the Niakhar study area in Senegal were followed prospectively between January 1984 and December 1996 for the occurrence of pertussis. Morbidity and mortality rates were extremely high before the launch of immunization. Crude incidence was 183 per 1,000 child-years at risk under age 5 years, with a 2.8% case-fatality rate. After the introduction of the vaccination program, overall incidence dropped rapidly and dramatically-by 27% after 3 years and 46% after 6 years. The decline in incidence involved all age groups but was most substantial in the group under age 5 years and was particularly pronounced in unvaccinated infants. The median age of acquisition of the disease rose steadily with population vaccine coverage. This study shows the tremendous magnitude of the disease burden in children and the rapid decline after vaccination, and it suggests a strong herd-immunity effect.*

**Rohani P, Earn DJ, Grenfell BT. Opposite patterns of synchrony in sympatric disease metapopulations. Science. 1999 Oct 29;286(5441):968-71.**

*Measles epidemics in UK cities, which were regular and highly synchronous before*

vaccination, are known to have become irregular and spatially uncorrelated in the vaccine era. Whooping cough shows the reverse pattern, namely a shift from spatial incoherence and irregularity before vaccination to regular, synchronous epidemics afterward. Models show that these patterns can arise from disease-specific responses to dynamical noise. This analysis has implications for vaccination strategies and illustrates the power of comparative dynamical studies of sympatric metapopulations.

## Vaccine efficacy, herd effects and duration of protection

**Jefferson T, Rudin M, DiPietrantonj C. Systematic review of the effects of pertussis vaccines in children. *Vaccine*. 2003 May 16;21(17-18):2003-14.**

*OBJECTIVE: To assess the efficacy and safety of whole-cell and acellular pertussis vaccines administered to children singly or within diphtheria, tetanus and pertussis (DTP) vaccines. DATA SOURCES: We searched the Cochrane Library, MEDLINE, EMBASE, Biological Abstracts and Science Citation Index to December 2001. Specialised websites and bibliographies of retrieved articles and reviews were assessed. Vaccine manufacturers and investigators were contacted for additional data. REVIEW METHODS: We included randomised and cohort studies comparing efficacy and/or safety of pertussis vaccines with placebo, DT, no intervention or each other. RESULTS: We included 52 studies (49 randomised controlled trials (RCTs), 3 cohort studies). All tested whole-cell and acellular vaccines were significantly more effective than placebo against pertussis. Absolute efficacy of whole-cell DTP varied from 37 to 92%. One- and two-component acellular vaccines had lower absolute efficacy (67-70%), than vaccines with  $\geq 3$  components (80-84%). Whole-cell vaccines were associated with significantly higher incidences of swelling and induration (odds ratio (OR) 11.67, 95% confidence interval (CI) 8.83-15.44), fever (OR for fever  $>39$  degrees C 3.36, 95% CI 2.06-5.49) and crying for  $>2$ h (OR 4.72, 95% CI 2.94-7.59) than placebo or DT. Differences in incidence of hypotonic hyporesponsive episodes (HHE) and convulsions were not statistically significant. Acellular pertussis vaccines did not cause a higher incidence of local signs, fever, convulsions, HHE or prolonged crying than placebo or DT. CONCLUSION: All tested pertussis vaccines were efficacious. Whole-cell vaccines show variable efficacy, making interpretation of direct comparisons unreliable. Acellular vaccines with  $\geq 3$  antigenic components showed higher efficacy than one- and two-component vaccines. The adverse event profile of acellular vaccines was similar to that of placebo and considerably better than that of whole-cell vaccines.*

**Preziosi MP, Halloran ME. Effects of pertussis vaccination on transmission: vaccine efficacy for infectiousness. *Vaccine*. 2003 May 16;21(17-18):1853-61.**

*We estimated the effect of pertussis vaccination on reducing transmission from vaccinated breakthrough cases from a comprehensive follow-up of a community of 30,000 residents in Niakhar, Senegal. Using a wide spectrum of case definitions,*

*vaccine efficacy was estimated as 1 - the ratio of secondary attack rates (SAR) in all households with cases during the calendar year 1993, a pertussis epidemic year. Vaccine efficacy for infectiousness (VEi) was 85% (95% confidence interval (CI), 46-95%) for children vaccinated with three doses of a whole-cell (WC; 94%) or an acellular (6%) pertussis vaccine, with pertussis defined as a cough  $\geq 21$  days with paroxysms confirmed by culture, serology, or contact with a culture-confirmed person. It was high for all case definitions. Partial vaccination reduced infectiousness. Pertussis vaccination is highly effective in reducing transmission from vaccinated breakthrough cases.*

**Preziosi MP, Halloran ME. Effects of pertussis vaccination on disease: vaccine efficacy in reducing clinical severity. Clin Infect Dis. 2003 Sep 15;37(6):772-9.**

*We estimated the effectiveness of pertussis vaccination in reducing the clinical severity of breakthrough disease among vaccinated individuals from a comprehensive follow-up study of a community of 30,000 residents of Niakhar, Senegal, in 1993. A physician examined all children with potential pertussis (cough of  $>7$  days' duration). Samples were collected from 97% of these children for culture or serologic testing as part of the active surveillance for a pertussis vaccine trial. Cases of pertussis were defined by confirmation through culture or serologic testing or by a history of contact with a person with culture-confirmed pertussis. Among children with confirmed cases, severity of illness was assessed according to a scale that combined clinical signs and symptoms. The efficacy of the vaccine in reducing disease severity was 48% (95% confidence interval, 39%-55%) among children vaccinated with 3 doses of whole-cell (67%) or acellular (32%) vaccine. Primary cases were more severe than secondary cases in residential compounds. Pertussis vaccination is effective in reducing the severity of illness.*

**Taranger J, Trollfors B, Bergfors E, Knutsson N, Lagergard T, Schneerson R, Robbins JB. Immunologic and epidemiologic experience of vaccination with a monocomponent pertussis toxoid vaccine. Pediatrics. 2001 Dec;108(6):E115.**

*Pertussis re-emerged in Sweden with a cumulative incidence of about 60% during the first 10 years of life, when the locally produced cellular vaccine lost its efficacy around 1970 and general vaccination was discontinued in 1979. The epidemiology, clinical features, and immunology of pertussis and a monocomponent pertussis toxoid vaccine were studied in Goteborg, Sweden. After phase 1 and 2 studies, a randomized, double-blind, placebo-controlled trial of pertussis toxoid (PTox), compounded with diphtheria and tetanus toxoids, was administered to 3450 children according to the Swedish schedule at 3, 5, and 12 months of age. After a mean follow-up of 18 months, the efficacy was 71% overall and 75% in household contacts, respectively. A statistically significant correlation was found between the level of PTox-induced antibodies and protection against pertussis. As observed with cellular and with multicomponent acellular vaccines, PTox reduced the severity of disease and the percent of children with positive cultures. Furthermore, vaccination reduced the transmission of *Bordetella pertussis* to household contacts in the vaccinees compared with the controls who received only diphtheria and tetanus toxoids. Patients with culture-verified *Bordetella parapertussis* infection reacted with antibodies to pertactin*

*and to filamentous hemagglutinin but not to pertussis toxin, and some subsequently developed pertussis. The antibody responses of patients with pertussis to the surface polysaccharides of B pertussis and to B parapertussis were cross-reactive serologically. Serosurveys showed that only antibodies to pertussis toxin were related to the occurrence of pertussis in the general population: antibodies to filamentous hemagglutinin and pertactin were probably stimulated by antigens of other bacteria as well as Bordetellae. Mass vaccination of Goteborg children born in the 1990s was started in 1995. In February 1999, about 55% had been vaccinated and both B pertussis and pertussis decreased significantly in individuals of all ages (herd immunity). Similar to diphtheria, PTox-induced immunity to pertussis occurs both on an individual and community basis. The apparent greater efficacy of multicomponent acellular pertussis vaccines compared with monocomponent PTox was proposed to be an artifact created when the diagnosis of pertussis was made by the serologic criteria of the World Health Organization only. Our conclusion is that PTox is both an essential and alone sufficient antigen in acellular pertussis vaccines.*

**Tran Minh NN, He Q, Edelman K, Putto-Laurila A, Arvilommi H, Viljanen MK, Mertsola J. Immune responses to pertussis antigens eight years after booster immunization with acellular vaccines in adults. Vaccine. 2000 Apr 3;18(19):1971-4.**

*Pertussis-specific antibody and cell-mediated immune (CMI) responses were studied in adults 8 years after booster immunization with either a bicomponent (pertussis toxin and filamentous hemagglutinin) or a monocomponent (pertactin) acellular vaccine and in age-matched healthy controls. The levels of vaccine-induced antibodies were also compared between the serum samples collected before, 1 month, 4 years, and 8 years after immunization. Over the follow-up period, geometric mean values (GMV) of antibodies to the vaccine antigens decreased in both groups of vaccinees. However, the 8-year postimmunization GMV were 3-20 times higher than preimmunization GMV (all P values <0.01). Moreover, both antibody and CMI responses to the vaccine antigens were significantly higher in the vaccinees than in the controls (all P<0.01 for antibody; all P<0.001 for CMI responses). The results show that antibody and CMI responses induced by acellular pertussis vaccines can persist for up to 8 years after booster immunization of adults primed with whole-cell vaccine.*

## Vaccine policy issues, including booster immunizations

**Campins-Marti M, Cheng HK, Forsyth K, Guiso N, Halperin S, Huang LM, Mertsola J, Oselka G, Ward J, Wirsing von Konig CH, Zepp F; International Consensus Group on Pertussis Immunisation. Recommendations are needed for adolescent and adult pertussis immunisation: rationale and strategies for consideration. Vaccine. 2001 Dec 12;20(5-6):641-6.**

*Pertussis vaccination of infants has dramatically reduced disease, complications and deaths in infancy and early childhood. But there is still a major public health challenge--to deal with the morbidity and economic burden of illness in older*

*children, adolescents and adults. Furthermore, it is these groups that form a major source of infection for non-immunised and partially immunised infants who are at high risk of severe complications. Adult-type acellular pertussis vaccine confers safe and effective protection against pertussis. There are several strategies to consider for immunising older individuals. Universal vaccination of all age groups would be the best available strategy for protecting individuals. It would also reduce the potential for transmitting the disease to other susceptibles, particularly infants. However, such a policy may be difficult both logistically and economically at this time. More easily achievable as a first step would be a strategy of universal adolescent booster vaccination combined with a programme targeted at adults most likely to have contact with very young babies including healthcare and childcare workers, parents and close family contacts. There is also potential for offering vaccination to adults (and their carers and close contacts) whose medical conditions or advanced age may place them at increased risk of more severe pertussis disease. Specific details of immunisation programmes must be made on a country by country basis depending on local circumstances.*

**Campins-Marti M, Moraga-Llop FA. Acellular pertussis vaccines for use among infants and young children. Expert Opin Pharmacother. 2004 Apr;5(4):807-17.**

*Pertussis is still one of the most common vaccine-preventable childhood diseases in developed countries. Infants, particularly those < 6 months, are the most susceptible and those who suffer the greatest disease burden and mortality. In the 1970s, concerns about the reactogenicity of whole-cell vaccines led to a decrease in vaccine coverage and later the re-emergence of the disease in many countries. The advent of acellular vaccines in recent years has constituted an important advance in the acceptance of this immunisation and consequently the control of the disease. The efficacy of acellular pertussis vaccines is approximately 59 - 93%, similar to whole-cell vaccines, but all available data confirm the substantial improvement in safety of the new vaccines. With the licensure of acellular pertussis vaccines and combined vaccines containing them, pertussis immunisation has become significantly developed. Furthermore, the possibility of continuing to vaccinate adolescents and adults with new diphtheria, tetanus, and pertussis (dTdap) vaccines is an important step in achieving control and elimination of the disease.*

**Edwards KM. Pertussis: an important target for maternal immunization. Vaccine. 2003 Jul 28;21(24):3483-6.**

*Cord blood antipertussis IgG concentrations were measured in infants and were found to be nearly equal to maternal levels. By 4 months of age most infants had no measurable antibody to pertussis toxin (PT) or filamentous hemagglutinin. Higher concentrations of maternally derived antibody to PT were associated with a weaker pertussis toxin antibody response to whole cell pertussis vaccine, but not to a cellular vaccine. These studies suggest that maternal immunization would provide early protection of the newborn to allow time for the primary immunization schedule at 2, 4,*

and 6 months of age to induce more durable protection.

**von Konig CH, Halperin S, Riffelmann M, Guiso N. Pertussis of adults and infants. Lancet Infect Dis. 2002 Dec;2(12):744-50.**

*Bordetella pertussis continues to circulate even in populations where a high vaccine coverage of infants and children is achieved. Cases in adolescents and adults are reported with increasing frequency in many countries. Adults are a reservoir for infections in very young infants, in whom pertussis may be severe and life-threatening. The salient clinical feature of pertussis in adolescents and adults is prolonged coughing, and recognising that pertussis does occur in these age groups is the most important step in its diagnosis. A laboratory diagnosis can be made by bordetella-PCR from nasopharyngeal swabs or secretions and by detection of antibodies, mainly to pertussis toxin; laboratory diagnosis is, however, not well standardised. Vaccination of adolescents and adults is now possible with acellular pertussis vaccines, which are well tolerated, immunogenic, and effective. Adolescent boosters and the vaccination of health-care workers are already included in vaccination calendars in some countries. Vaccine-recommending bodies and national health-care organisations must have locally relevant information on the transmission of pertussis from adults to infants to be able to make decisions on the advisability, feasibility, and priority for booster immunisation against pertussis.*

## Other issues related to pertussis vaccination

**Fung KS, Yeung WL, Wong TW, So KW, Cheng AF. Pertussis - a re-emerging infection? J Infect. 2004 Feb;48(2):145-8.**

*Seven cases of pertussis in patients aged between 1 and 6 months detected over 3 months were reported. Paroxysmal cough (six cases), post-tussive vomiting (three cases) and poor feeding (three cases) were the most common presenting symptoms. Bordetella pertussis was isolated from six patients. The total leucocyte counts were mildly increased ( $10.8-15.6 \times 10^9/L$ ). The lymphocyte counts were markedly raised (59-73%) and appear to be useful indicators of pertussis. It appears that herd immunity does not offer adequate protection to the vulnerable group even in well-vaccinated populations. High vaccination coverage should be maintained, and vaccination should be given as early an age as possible. Aggressive efforts to identify cases and contacts are essential. Health care workers should have a high index of suspicion for pertussis, in particular for those with paroxysmal cough and high lymphocyte counts so as to give timely diagnosis and treatment.*

**De Serres G, Shadmani R, Duval B, Boulianne N, Dery P, Douville Fradet M, Rochette L, Halperin SA. Morbidity of pertussis in adolescents and adults. : J Infect Dis. 2000 Jul;182(1):174-9. Epub 2000 Jun 30.**

*The effect of age on the clinical presentation of pertussis was assessed in 664 adolescent and adult cases. Complications were more frequent in adults than in*

*adolescents (28% vs. 16%). Pneumonia occurred in 2% of patients <30 years old but in 5%-9% of older patients. Urinary incontinence occurred in 34% of women ≥50 years old. Duration of cough, risk of sinusitis, and number of nights with disturbed sleep increased with smoking and asthma. The secondary attack rate in other household members ≥12 years was 11%. Pertussis in secondary case patients was less severe than in index case patients but presented with classic symptoms. The main source of infection in adolescents was schoolmates or friends; in adults it was workplace or their children. Teachers and health care workers had a greater risk of pertussis than did the general population. The burden of disease appears to increase with age, with smoking, and with asthma.*

**Olin P, Hallander HO, Gustafsson L, Reizenstein E, Storsaeter J. How to make sense of pertussis immunogenicity data. Clin Infect Dis. 2001 Dec 15;33 Suppl 4:S288-91.**

*Studies on serologic correlates to protection in pertussis were reviewed. Trials in the 1950s showed that agglutinin titers correlated to protection of whole-cell vaccines, but postvaccination antibodies against pertussis toxin (PT) and against filamentous hemagglutinin did not in a later trial of acellular vaccines. However, in household studies nested in 2 recent trials, preexposure antibody levels against pertactin and against fimbriae correlated with protection against typical and mild pertussis, and anti-PT correlated only with protection against typical pertussis. These findings could be used by regulatory agencies to license pertussis vaccines. A reference laboratory for pertussis should distribute panels to control interlaboratory variation in recommended assays, and a minimal response should be set for each pertussis antigen. We conclude that 2 studies have shown correlates between measurable anti-pertactin, anti-fimbriae, and anti-PT antibody levels at exposure and individual protection against pertussis. We suggest that postvaccination response rates may be used as surrogate markers of protection.*

**Smith AM, Guzman CA, Walker MJ. The virulence factors of Bordetella pertussis: a matter of control. FEMS Microbiol Rev. 2001 May;25(3):309-33.**

*Bordetella pertussis is the causative agent of whooping cough, a contagious childhood respiratory disease. Increasing public concern over the safety of whole-cell vaccines led to decreased immunisation rates and a subsequent increase in the incidence of the disease. Research into the development of safer, more efficacious, less reactogenic vaccine preparations was concentrated on the production and purification of detoxified B. pertussis virulence factors. These virulence factors include adhesins such as filamentous haemagglutinin, fimbriae and pertactin, which allow B. pertussis to bind to ciliated epithelial cells in the upper respiratory tract. Once attachment is initiated, toxins produced by the bacterium enable colonisation to proceed by interfering with host clearance mechanisms. B. pertussis co-ordinately regulates the expression of virulence factors via the Bordetella virulence gene (bvg) locus, which encodes a response regulator responsible for signal-mediated activation and repression. This strict regulation mechanism allows the bacterium to express different gene subsets in different environmental niches within the host, according to the stage of disease progression.*

