

Updated WHO position paper on pertussis vaccines

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World Health
Organization

Introduction

- Replaces the position paper on pertussis vaccines published in the *Weekly Epidemiological Record* in January 2005
- Incorporates recent developments in the field of pertussis vaccines and current WHO recommendations for their use
- Provides a limited number of core references and a link to a more comprehensive reference list
- Offers links to grading tables assessing the quality of scientific evidence for key recommendations



Background information

- Each year, *Bordetella pertussis* causes an estimated 16 million cases of whooping cough and about 195 000 deaths, mainly among infants in developing countries
- Large-scale vaccination during the 1950s–1960s resulted in >90% reduction in pertussis incidence and mortality in the industrialized world
- About 82% of all infants worldwide are receiving 3 doses of pertussis vaccine. It is estimated that in 2008, global vaccination against pertussis averted about 687 000 deaths



Pertussis vaccines

- Two types of pertussis vaccines: whole-cell (wP) and acellular (aP) vaccines
wP and aP are usually offered in fixed combinations with diphtheria toxoid and tetanus toxoid (DPwP/DTaP); some combinations also include vaccines against poliomyelitis, hepatitis B, and *Haemophilus influenzae* type b
- Primary series of wP and aP consists of 3 doses given in infancy. National immunization schedules vary considerably. (For WHO recommended schedule, see after)
- Following the primary series, the best wP and aP vaccines show similar efficacy/effectiveness (80-90%) against severe pertussis.
- Significant heterogeneity across studies complicates comparisons of the different vaccines
- Except for rare anaphylactic reactions that may follow wP- or aP-administration, there are no contraindications to their use



Whole-cell pertussis vaccines

- wP are based on standardized cultures of selected *B. pertussis* strains, that are subsequently killed
- Each lot of vaccine undergoes extensive testing to assess potency, toxicity, sterility, and bacterial concentration
- Production methods vary between manufacturers and hence, wP vaccines are relatively heterogeneous
- All wP- vaccines contain aluminium salts as an adjuvant and some have thiomersal or other preservatives for multidose presentations
- wP-containing vaccines must not be frozen, but should be stored at 2–8 °C



Safety of wP vaccines

- Injections of wP vaccines are frequently (1 in 2–10) associated with local redness and swelling, induration, fever and agitation
- Prolonged crying and febrile convulsions occur in <1 in 100, hypotonic-hyporesponsive episodes in <1 in 1000–2000
- To date, no evidence that wP vaccines cause brain damage or any severe neurological disorder
- Local reactions tend to increase with age and number of injections; wP-containing vaccines are not recommended for adolescents and adults



Acellular pertussis vaccines

- aP vaccines contain 1 - 5 of the following bacterial components:
- pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin (PRN), fimbriae (FIM) types 2 and 3, adenylate cyclase toxin (ACT), tracheal cytotoxin (TCT), lipooligosaccharide (LOS) and *B. pertussis* endotoxin
- Exact contribution of the different antigens to protection is not clear
- Current aP vaccines differ in number of antigen components, choice of clone for primary antigen production, purification and detoxification, adjuvants, and preservatives such as thiomersal
- aP-containing vaccines must not be frozen, but be stored at 2–8 °C



Safety of aP vaccines

- aP vaccines are less reactogenic than wP vaccines and frequency of adverse events following primary aP vaccination equals that of control groups, regardless of number of components
- After primary series, local reactions tend to increase in rate and severity with each subsequent DTaP dose
- After booster doses of aP-containing vaccines, transient, benign and painless swelling sometimes involving the entire limb occurs in 2% to 6% of children . The swelling always subsides spontaneously without any sequelae
- To reduce reactogenicity of booster injections, aP-containing vaccines with reduced antigen concentration have been formulated for use in adolescents and adults



Duration of protection and booster doses in children

- In the industrialized world, vaccine induced protection wanes after 4–12 years and pertussis is increasingly reported in older children, adolescents and adults
- For example, in the United States of America there has been a remarkable recent increase in the incidence of pertussis among aP-vaccinated children aged 7-10 yrs
- These data suggest that at least with aP-containing vaccines used in low-incidence settings, a 3-dose primary series with a booster in 2nd year of life provide insufficient protection against pertussis in children >6 years, and that another booster may be needed at the time of school entry



Economic considerations

- Literature on cost-effectiveness of immunizing against pertussis very limited, particularly in developing countries
- In 1999, a mathematical model based on universal use of aP vaccination in Italy suggested that increases in coverage $> 50\%$ yielded health gains at modest net costs, and coverage rates of 90% resulted in direct net savings of US\$ 42 per additional vaccinee
- In the UK, a pre-school booster of pertussis vaccine was predicted to reduce morbidity and mortality in the younger age groups by 40-100% with a likely cost per life-year gained of $< 10,000$ British pounds (2002)
- Higher development and production costs of aP-containing vaccines result in prices per dose that are higher than prices for wP-containing vaccines. Therefore, aP-containing vaccines are unlikely to be currently affordable in most developing countries



WHO position on the use of pertussis vaccines (1)

- The main aim of pertussis vaccination is to reduce the risk of severe pertussis in infancy
- At least 90% coverage with 3 doses of high quality pertussis vaccines in infants remains the programme priority worldwide, particularly where pertussis still poses a serious health problem in infants and young children



WHO position on the use of pertussis vaccines (2)

Choice of vaccines

- Protection against severe pertussis in infancy and early childhood can be obtained after a primary series of wP or aP vaccination
- Although local and systemic reactogenicity is more commonly associated with wP-containing vaccines, both aP and wP-containing vaccines have an excellent safety record with regard to serious adverse events
- aP-containing vaccines are significantly more expensive than wP-containing vaccines. For many countries there is insufficient marginal benefit to consider changing from wP to aP-containing vaccines
- In countries where the higher non-serious reactogenicity of wP would be an impediment to high vaccination coverage, use of aP may be a mechanism to improve acceptability. In those cases, aP should replace the wP vaccine in the national childhood immunization programme, either for the booster dose only or for the entire vaccination series



WHO position on the use of pertussis vaccines (3)

Primary vaccination

- WHO recommends a 3-dose primary series with the first dose administered at 6 weeks of age, and subsequent doses given 4-8 weeks apart, at 10-14 and 14-18 weeks of age
- The last dose of the recommended primary series should be completed by the age of 6 months
- All infants, including HIV-positive individuals, should be immunized against pertussis
- Although administration of aP vaccine at birth and at one month has been shown to induce antibody responses in infants at the age of 2 months further studies are needed to confirm this finding and neonatal immunization against pertussis is not currently part of the WHO recommendations



WHO position on the use of pertussis vaccines (4)

Booster doses and interrupted vaccination series

- The duration of protection following primary immunization varies considerably depending upon factors such as local epidemiology, schedule & choice of vaccine
- A booster dose is recommended for children 1- 6 years of age, preferably during the second year of life in order to improve protection following primary immunization, provide an opportunity for catch-up vaccination, and allow for use of a combination vaccine containing both pertussis and Hib antigens
- The booster should be given at least 6 months after the last primary dose
- Completion of this schedule (primary series plus booster) is expected to ensure protection against pertussis for at least 6 years
- Children whose vaccination series has been interrupted should have their series resumed, without repeating previous doses. Children 1 to <7 years of age with no previous immunization should receive 3 doses of wP or aP vaccine with intervals of 2 months between 1st and 2nd dose, and 6-12 months between 2nd and 3d dose



WHO position on the use of pertussis vaccines (5)

Boosters of pertussis vaccine in adolescents and adults

- Although vaccination can prevent pertussis in adolescents and adults there is insufficient evidence to support the addition of vaccine boosters in these age groups for achieving the primary goal of reducing severe pertussis in infants
- Decisions concerning such programmes should be based on relevant disease incidence and cost-effectiveness data and embarking on this strategy presupposes high coverage of routine infant immunization
- The duration of protection following a single adolescent booster as well as programmatic costs and implications merit further investigation
- Only aP-containing vaccines should be used for vaccination against pertussis in age groups > 6 years



WHO position on the use of pertussis vaccines (6)

Vaccination of pregnant women and household contacts

- There is currently insufficient evidence to recommend pertussis vaccination of pregnant women
- Although several countries have recommended vaccination of close household contacts and caregivers (“cocooning”), significant programmatic difficulties and unproven effectiveness have led WHO to conclude that so far, there is inadequate evidence to recommend this strategy
- The relative merits of neonatal vaccination versus maternal vaccination should be investigated.



WHO position on the use of pertussis vaccines (7)

Vaccination of health-care workers

- Vaccination of health-care workers, primarily to prevent nosocomial transmission of pertussis to infants and immunocompromised persons, is possibly cost-effective if high coverage rates are obtained
- In most settings high coverage is unlikely without measures to both enhance access to and compliance with recommendations
- Countries with demonstrable nosocomial transmission are encouraged to implement such vaccination with emphasis on maternity and paediatric staff, if economically and logistically feasible



WHO position on the use of pertussis vaccines (8)

Vaccine interchangeability and combinations

- Interchanging between or within the wP and aP vaccine groups is unlikely to interfere with safety or immunogenicity of these vaccines
- Surveillance should be implemented in countries that introduce vaccine combinations, especially when aP-containing combinations are used



WHO position on the use of pertussis vaccines (9)

Surveillance

- Careful epidemiological surveillance of pertussis, particularly laboratory-confirmed disease, is encouraged worldwide to monitor disease burden and the impact of immunization
- Of particular interest are surveys comparing age-specific incidences of pertussis in countries with different vaccine booster policies. Outbreak studies may also offer valuable information and should be encouraged. When results are available WHO will review current maternal vaccination studies using aP-containing vaccines
- Existing research platforms including the Child Health Epidemiology Reference Group, the Pneumonia Etiology Research for Child Health project and the Neonatal Sepsis Etiology Trial should be expanded to better understand the true burden of infant pertussis

