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Core information for the development of immunization policy

2002 update

Vaccines and Biologicals

World Health Organization

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Abbreviations

AFP	acute flaccid paralysis
AIDS	acquired immune deficiency syndrome
aP	acellular pertussis
CRS	congenital rubella syndrome
DT	diphtheria–tetanus (vaccine)
DTP	diphtheria–tetanus–pertussis (vaccine)
EPI	Expanded Programme on Immunization (WHO)
HAV	hepatitis A virus
HBV	hepatitis B virus
HepB	hepatitis B
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
IPV	inactivated polio vaccine
JE	Japanese encephalitis
MCC	Group C meningococcal conjugate (vaccine)
MM	measles–mumps (vaccine)
MMR	measles–mumps–rubella (vaccine)
NID	national immunization day
OPV	oral polio vaccine
RRV	rhesus rotavirus vaccine
SNID	subnational immunization day
TB	tuberculosis
TT	tetanus toxoid
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
V&B	Department of Vaccines and Biologicals (WHO)
VZV	varicella-zoster virus
WHO	World Health Organization
wP	whole-cell pertussis

Introduction

The Expanded Programme on Immunization (EPI) has published two earlier versions of a document outlining how national programmes might best use vaccines in their infant immunization service. Since the last revision in 1995, much has changed in the world of vaccines. This updated document provides concise background information that will assist national planners to formulate policies on the use of previously used and many new vaccines. The information is provided systematically on a greater number of vaccines, many of which have recently had position papers published in the *Weekly Epidemiological Record* that go into more detail about the vaccines and how to use them.

As a general rule, vaccines for large-scale public health use should:

- Meet the quality requirements as defined in the current WHO policy statement on vaccine quality.
- Be safe and have a significant impact on the actual disease in all target populations.
- If intended for infants or young children, be easily adapted to the schedules and timing of the national childhood immunization service.
- Not interfere significantly with the immune response to other vaccines given simultaneously.
- Be formulated to meet common technical limitations, e.g. in terms of refrigeration and storage capacity.
- Be appropriately priced for different markets.

Since the inception of EPI, each vaccine has been selected on the basis of safety, effectiveness, reasonable price and the ability to combat a childhood disease of significant global public health importance. The six vaccine-preventable diseases originally targeted in 1974 were tuberculosis, poliomyelitis, diphtheria, pertussis, tetanus and measles. Hepatitis B was added later, and yellow fever was added for countries where this disease is endemic. Most recently, *Haemophilus influenzae* type b (Hib) vaccine was introduced in 1998. Table 1 summarizes the information on the vaccine-preventable diseases of greatest relevance to the design of control services. Although many other vaccines are now available or under development, this document has only been able to cover the most important ones from a public health perspective. Other position papers covering actual or candidate vaccines are in preparation and will be included in future revisions as appropriate.

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Table 1. Epidemiology of selected vaccine-preventable diseases

Disease	Agent	Reservoir	Spread	Transmission period	Subclinical infection	Duration of natural immunity	Risk factors for infection
Tuberculosis	Mycobacterium tuberculosis	Humans	Airborne droplet nuclei from sputum-positive persons	As long as sputum acid-fast bacilli positive	Common but not important in transmission	Not known Reactivation of old infection commonly causes disease	• Low socioeconomic status • Poor access to care • Immunodeficiency • Malnutrition • Alcoholism • Diabetes
Diphtheria	Toxin-producing bacterium (Corynebacterium diphtheriae)	Humans	Close respiratory or cutaneous contact	Usually under 2 weeks Some chronic carriers	Common	Lasting protection but some evidence of waning	• Crowding • Low socioeconomic status
Hib	Bacterium (Haemophilus influenzae type b)	Humans	Close respiratory contact	Chronic carriage for months	Common	Lifelong	• Failure to breastfeed • Crowding • Low socioeconomic status
Hepatitis B	Virus	Humans	Blood, e.g. perinatal, household, occupational, sexual	Chronic carriers for a long time, possibly for life	Common, especially in infants	If develops, lifelong	• HBeAg+ mother • Multiple sexual partners • Intravenous drug use
Measles	Virus	Humans	Close respiratory contact and aerosolized droplets	4 days before rash until 2 days afterwards	May occur, but relative importance unknown	Lifelong	• Crowding • Low socioeconomic status
Pertussis	Bacterium (*Bordetella pertussis*)	Humans	Close respiratory contact	Usually under 3 weeks (starts before whoop is apparent)	Mild illness common: may not be diagnosed	Prolonged protection	• Young age • Crowding
Poliomyelitis	Virus (serotypes 1, 2 and 3)	Humans	Faecal–oral, close respiratory contact	Few days before and after acute symptoms	>100 subclinical infections for each paralytic case	Lifelong type-specific immunity	• Poor environmental hygiene
Tetanus	Toxin-producing bacterium (*Clostridium tetani*)	Animal intestines Soil	Spores enter body through wounds/ umbilical cord	No person-to-person transmission	No	Lasting protective immunity not produced by infection: second attack possible	• Soil-contaminated wound, umbilical cord • Agricultural work
Yellow fever	Virus	Monkeys and humans	Bite by infected mosquitoes	Infected individuals can transmit the disease when bitten by a mosquito vector during the viraemic phase (the first 3–4 days of illness)	Common	Lifelong	• Young age • Forest workers • Season (late rainy season, early dry season)

Table 2. Characteristics of selected vaccines

Disease	Nature of vaccine	Minimum potency per dose (as defined in WHO requirements)	Form	Adjuvant	Stabilizer	Preservative	Number of doses* and route	Heat stability
Tuberculosis	BCG Attenuated *Mycobacterium bovis*	At least 50 000 particles	Freeze-dried	None	e.g. sodium glutamate	None	1 i.d.	Medium in dried form, low in reconstituted form
Diphtheria	Toxoid	At least 30 IU	Liquid	$Al(OH)_3/AlPO_4$	None	Usually thiomersal (or 2-phenoxyethanol)	3 i.m.	High
Tetanus	Toxoid	At least 40 IU in TT and 60 IU for T component in DTP when tested in mice	Liquid	$Al(OH)_3/AlPO_4$	None	Usually thiomersal (or 2-phenoxyethanol)	3 i.m.	High
Pertussis	Killed whole-cell pertussis bacterium	At least 4 IU	Liquid	$Al(OH)_3/AlPO_4$	None	Usually thiomersal (or 2-phenoxyethanol)	3 i.m.	Medium
Polio	Attenuated live polio viruses of 3 types	Type 1: 10^6 $CCID_{50}$ Type 2: 10^5 $CCID_{50}$ Type 3: $10^{5.8}$ $CCID_{50}$	Liquid	None	Magnesium chloride or sucrose	Small amount of antibiotic	3 or 4 oral	Low
Measles	Attenuated live virus	At least 1000 $CCID_{50}$	Freeze-dried	None	Depends on producer	Small amounts of antibiotics	1 s.c.	Medium in dried form, low once reconstituted
Hib	Capsular polysaccharide linked to protein (toxoid or other)	At least 10 mcg of capsular polysaccharide conjugated to protein	Liquid or freeze-dried	Most have no adjuvant, some have $Al(OH)_3/AlPO_4$	e.g. lactose	Thiomersal or 2-phenoxymethanol in multidose vials, but may be absent from monodose preparations	3 i.m.	High
Hepatitis B	HBsAg	Varies with manufacturer	Liquid	$Al(OH)_3/AlPO_4$	None	Thiomersal or 2-phenoxyethanol, but may be absent in monodose preparations	3 i.m.	High
Yellow fever	Attenuated live virus	At least 1000 mouse LD_{50}	Freeze-dried	None	Small amounts of antibiotics and stabilizers	Small amounts of antibiotic	1 s.c.	Medium in dried form, low once reconstituted

IU = international units of potency as determined in animal tests
Mcg = microgramme
Infectious units – $CCID_{50}$ (cell culture infective dose 50%): the quantity of a virus suspension that will infect 50% of cell cultures
– Mouse LD_{50}: Lethal dose $_{50}$ = 50% of mice will die if given this dose
No. of doses in EPI-recommended primary schedule; route: i.d. = intradermal; i.m. = intramuscular (some countries use deep subcutaneous injections); s.c. = subcutaneous.

Table 3. Vaccine efficacy and vaccine-induced immunity

Vaccine (number of doses)	Vaccine efficacy	Nature of protective antibodies and protective level of antibodies*	Duration of immunity after primary series	Comments
BCG (1)	0%–80% for pulmonary tuberculosis (TB) 75%–86% for meningitis and miliary TB	Not known; immunological response includes cell-mediated immunity	Unknown; some evidence that immunity wanes with time	Reasons for varying efficacy multifactorial
Diphtheria toxoid (3)	>87% (no data from developing countries)	Antitoxin; 0.01 IU/ml by neutralization test	Variable: probably around 5 years; longer in presence of natural boosting or booster doses	Recent trends to lower antibody levels in adults because of less natural boosting
Tetanus toxoid (3)	>95% (>80% after two doses) in infants	Antitoxin; 0.01 IU/ml by neutralization test	Five years	5 doses in adults provide protection for over 20 years
Pertussis (3)	Estimates vary widely because the products vary; efficacy higher against severe disease (in most instances at least 80% protection against severe disease)	Immunity is probably provided by antibodies against different components of pertussis bacteria	Unknown; some evidence that it wanes with time	Immunological correlates of protection are lacking
Polio (3)	>90% in industrialized countries; 72%–98% in hot climates; lower protection against type 3	Neutralizing antibody; Detectable antibody thought to equal protection	Lifelong if boosted by wild virus; may be shorter when no wild virus circulating	Primary series may not give adequate protection in hot climates (interference from other viruses)
Measles (1)	>90% at 12 months of age >85% at 9 months of age	Neutralizing antibody; 200 mIU/ml by neutralization test	Lifelong if boosted by wild virus; may be shorter when no wild virus circulating	Lower efficacy when maternal antibody present
Hib (3)	>95% for invasive disease	Anticapsular antibodies; 1 mcg/ml	Unknown but lasts for at least 3 years beyond period of greatest exposure	
Hepatitis B (3)	75%–95%; efficacy against chronic infection	Antibody to surface antigen 10 mIU/ml	>15 years; further follow-up is continuing	Efficacy lower if injected into fat layer
Yellow fever (1)	90%–98%	Neutralizing antibody; Correlates with protection	For at least several decades, possibly for life	

* Best estimates of protective level of antibody when measured by neutralization tests; may not correlate well with other assays.

Infant immunization schedule (birth to 11 months)

Table 4 shows the immunization schedule recommended by the Expanded Programme on Immunization for developing countries. Whichever the national schedule, infants should be immunized as close as possible to the scheduled age with each vaccine in order to ensure the earliest possible protection against the target diseases. This is particularly important where the target diseases are endemic. Variation of the schedule in table 4 may be appropriate to meet specific epidemiological circumstances.

Table 4. Immunization schedule for infants recommended by the Expanded Programme on Immunization

Vaccine	Age				
	Birth	6 weeks	10 weeks	14 weeks	9 months
BCG	x				
Oral polio	x†	x	x	x	
DTP		x	x	x	
Hepatitis B Scheme A*	x	x		x	
Hepatitis B Scheme B*		x	x	x	
Haemophilus influenzae type b		x	x	x	
Yellow fever					x**
Measles					x***

† In polio-endemic countries

* Scheme A is recommended in countries where perinatal transmission of hepatitis B virus is frequent (e.g. in South-East Asia). Scheme B may be used in countries where perinatal transmission is less frequent (e.g. in sub-Saharan Africa).

** In countries where yellow fever poses a risk.

*** A second opportunity to receive a dose of measles vaccine should be provided for all children. This may be done either as part of the routine schedule or in a campaign.

Vaccines in pregnancy

- Animal studies are not particularly helpful in assessing the risk to the human fetus of vaccines administered in pregnancy. For this reason, except in specific cases, vaccination should be avoided in pregnancy, particularly during the first trimester. In some circumstances the risk of the vaccine must be weighed against the benefits of protection for the women and/or infants. The benefit of vaccinating pregnant women usually outweighs the risk when: the risk of disease exposure is high; or
- infection poses a special risk to the mother or fetus.

Killed inactivated vaccines, toxoids and polysaccharides have been administered to pregnant women and have not been associated with adverse outcomes. For example, the tetanus toxoid vaccine has been safely administered to pregnant women and has reduced the incidence of neonatal tetanus in large regions of the world. Inactivated influenza vaccine has been recommended for pregnant women beyond their first trimester or for those having medical conditions that increase the risk of complications from influenza. The vaccination of pregnant women is generally deferred until the third trimester in order to minimize the risks to the developing fetus and the risk of precipitating a miscarriage. Most live vaccines, such as BCG, measles, mumps, rubella and varicella, should not be administered during pregnancy in order to avoid potential risks of congenital anomalies and infection of the fetus. However, some live vaccines may be given to pregnant women at high risk of exposure (e.g. yellow fever and oral polio vaccines). In practice, rubella vaccine given inadvertently to pregnant women has not resulted in abnormalities, indicating that termination would not be appropriate in such cases. A study in Finland confirmed that it was safe to administer OPV to pregnant women in a mass campaign.

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Immunization of HIV-infected individuals

Public health strategies

The epidemic of human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) has had a number of implications for immunization services. With some notable exceptions, immunization is generally safe and beneficial for HIV-infected children. The majority of children born to HIV-infected women do not acquire HIV infection. However, identifying those who do contract the infection requires tests that are not readily available in most countries. Screening for HIV status should therefore not be carried out before immunization.

The efficacy of immunization is variable for HIV-infected individuals. The immune suppression caused by HIV may result in less benefit from the vaccine than for children who are not infected with the virus. Most HIV-infected children have the capacity to mount both cellular and humoral immune responses during the first two years of life; decline in these responses occurs during the next two years. Studies of the immunogenicity of recommended vaccines have shown satisfactory seroconversion rates in the early stages of infection. However, the proportion of responders decreases with progression from HIV infection to AIDS.

As HIV-infection results in a deterioration of the immune system, there has been concern that the use of live vaccines could result in severe vaccine-associated disease in those individuals. To date, there have been only rare and isolated reports of adverse reactions in HIV-infected persons to the live vaccines OPV and measles, and no increase in rates of reactions to DTP and hepatitis B vaccines (that contain no live organisms). Although simultaneous administration of multiple antigens (even inactivated vaccines) might theoretically accelerate the HIV disease process, clinical and laboratory data do not support this.

WHO perspective

The decreased immune response to vaccines with increasing age for HIV-infected children emphasizes the need for immunization as early in life as possible for children born to HIV-infected women. Individuals with symptomatic HIV infection can receive all the standard vaccines except for BCG and vaccine against yellow fever. As for any severely ill child, severely ill HIV-infected children should not be vaccinated.

Special issues

BCG: BCG should not be given to children with symptomatic HIV infection (i.e. AIDS). In asymptomatic children, the decision to give BCG should be based on the local risk of tuberculosis:

- Where the risk of tuberculosis is high, BCG is recommended at birth or as soon as possible thereafter, in accordance with standard policies for immunization of non HIV-infected children.
- In areas where the risk of tuberculosis is low but BCG is recommended as a routine immunization, BCG should be withheld from individuals known or suspected to be infected with HIV.

***Measles*:** Children with known or suspected HIV infection are at increased risk of severe measles and should be offered measles vaccine as early as possible. Such infants should receive measles vaccine at six months of age, followed by an extra dose at nine months. The overall risk to them of the vaccine causing adverse events is low compared with the risk of measles infection and its complications. Where the chance of contracting wild-type measles virus infection is almost non-existent, countries with the capacity to monitor an individual's immune status may consider withholding measles vaccine from severely immunocompromised, HIV-infected children, but children with moderate levels of immune suppression should continue to receive measles vaccine.

***OPV*:** Individuals with known or suspected HIV infection should be immunized with OPV according to standard schedules.

***Hepatitis B vaccine*:** Early immunization is especially important because the risk of becoming a chronic carrier is higher for HIV-infected children and adults than for uninfected persons.

***Yellow fever*:** Individuals with symptomatic HIV infection should generally not receive live, attenuated yellow fever vaccine. It should be withheld from HIV-symptomatic individuals until such time as more information is available on its safety when given to HIV-infected individuals. Where the risk from yellow fever disease is high, medical practitioners may consider the risk to an individual from the vaccine to be less than that from the disease, and may consider giving the vaccine.

***Varicella*:** The public health impact of varicella and zoster may be increasing in regions with high rates of HIV endemicity. Indications, including the results of vaccination studies in certain immunodeficient groups, are encouraging. The public health as well as the socioeconomic impact of this vaccine would increase drastically if proved to protect against zoster in the general population. In industrialized countries considerable amounts of money are spent on medical care in complicated cases of zoster in immunocompromised or elderly persons, and the increasing incidence of zoster in HIV-affected areas is well documented.

Table 5. Recommendations for the immunization of HIV-infected children and women of childbearing age

Vaccine	Asymptomatic HIV infection	Symptomatic HIV infection
BCG	Yes	**No**
DTP	Yes	Yes
OPV	Yes	Yes
Measles	Yes	Yes
H. influenzae type b	Yes	Yes
Hepatitis B	Yes	Yes
Yellow fever	Yes	**No***
Tetanus toxoid	Yes	Yes

* *Pending further studies*

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BCG vaccine

Public health strategies

Tuberculosis is caused by *Mycobacterium tuberculosis* and is estimated to result in 2.6 million deaths worldwide annually and 3.8 million notified cases. The initial infection is usually silent and may result in no further symptoms. Some cases progress to pulmonary TB and disseminated disease with meningeal or other extrapulmonary involvement. Although commonest in adults, the disease is usually more serious in infants, children and adolescents. Reasonable control of the disease was achieved until the 1980s in many countries through improved living standards (so that children were no longer sleeping in close proximity to parents with open pulmonary disease) coupled with antituberculous medication. With the deterioration of public health services in some countries, and with the advent of HIV infection, the numbers of cases escalated and new strategies were investigated. Directly observed treatment, short-course (DOTS) is the keystone of WHO's TB control strategies.

WHO perspective

A single dose of BCG should be given as soon as possible after birth in all populations at high risk as a means of minimizing the harmful effects of TB infection in the first year of life. The vaccine should be used until an alternative improved antituberculosis vaccine is available (probably at least a decade hence). In the meantime, national immunization services are encouraged to maintain the highest possible level of vaccination coverage of infants. Some countries where the risk of TB is low have chosen to administer BCG vaccine to school-age children. BCG should not be given in pregnancy.

BCG is given in the neonatal period to protect against severe forms of the disease (miliary spread and meningitis). A neonate has not experienced prolonged exposure to the disease by the time the vaccine is given, so no screening process is recommended. Neither radiography nor tuberculin skin testing can differentiate between exposed and non-exposed infants and such tests should be avoided. Skin testing may be appropriate later in life for diagnostic purposes or before the vaccination of health workers and other personnel at high risk.

Special issues

TB-infected mothers: Babies born to mothers who develop tuberculosis disease shortly before or shortly after delivery are not protected sufficiently quickly by BCG given at birth to avoid the possibility of becoming infected. Neonates should be given daily isoniazid (5 mg/kg) for six months as prophylactic chemotherapy. BCG, which is inactivated by chemotherapy, can be given after it ends.

Repeat (booster) vaccination: Booster doses should not be given. Many countries still recommend repeat vaccination but there is no evidence that it is effective.

Duration of effect: Too little is known of the duration of protection given by BCG. Information on this matter is essential for estimating the impact of BCG vaccination programmes.

High-risk subgroups: Many countries have a low prevalence of tuberculosis in the majority of their populations but still have small numbers of high-risk individuals, such as immigrants who have just arrived from places where the prevalence of the disease remains high. In such situations, BCG is offered only to infants at high risk.

HIV infection: BCG should not be given to children with symptomatic HIV infection (i.e. AIDS). In asymptomatic children, the decision to give BCG should be based on the local risk of tuberculosis:

- Where the risk of tuberculosis is high, BCG is recommended at birth or as soon as possible thereafter, in accordance with standard policies for immunization of non HIV-infected children.
- In areas where the risk of tuberculosis is low but BCG is recommended as a routine immunization, BCG should be withheld from individuals known or suspected to be infected with HIV.

In practice, few if any neonates are likely to have symptoms of HIV infection and should therefore receive BCG vaccine. Cases of BCG-itis in adult AIDS patients have suggested that viable BCG can remain for a long period in vaccinated individuals. The extreme rarity of these cases, however, after almost two decades of the HIV pandemic, favours the continuation of the present policy.

Criteria for discontinuation: Increasing numbers of developed countries are likely to shift from routine to selective BCG vaccination during the next decade. WHO supports the International Union Against Tuberculosis and Lung Disease (IUATLD)'s criteria that provide a rough guide for this decision. An efficient notification system must be in place, and one of the following:

- an average annual notification rate of smear-positive pulmonary tuberculosis below 5 per 100 000; or
- an average annual notification rate of tuberculous meningitis in children under five years of age below 1 per 10 million population over the previous five years; or
- an average annual risk of tuberculous infection below 0.1%.

Further work is needed on the cost-benefit ratio of BCG as opposed to that of other approaches to control. One argument favouring the discontinuation of BCG is based on the advantages inherent in the absence of non-specific BCG-induced tuberculin sensitivity. This would facilitate the use of tuberculin testing for contact tracing, source identification and the selection of individuals for preventive therapy. This is a valid argument but many years would have to elapse after the discontinuation of routine BCG vaccination before a vaccinated population could be completely replaced with unvaccinated individuals.

Administration summary

Type of vaccine	Live bacterial (BCG)
Number of doses	One given intradermally
Schedule	At or as soon as possible after birth (0.05 ml)
Booster	None
Contraindications	Symptomatic HIV infection
Adverse reactions	Local abscess, regional lymphadenitis; rarely, distant spread to osteomyelitis, disseminated disease
Special precautions	Correct intradermal administration is essential

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Cholera vaccine

Summary and conclusions

Throughout history, the waterborne and highly infectious bacterium *Vibrio cholerae* has caused devastating outbreaks in most parts of the world. The current pandemic is caused by the El Tor biotype of *V. cholerae,* serogroup O1, and started in South-East Asia in 1961. It has subsequently led to outbreaks in numerous countries in Asia, Africa and South America. Since 1992, *V. cholerae* O139, which is a new and more virulent serogroup variant of the El Tor biotype, has spread to many parts of Asia. In spite of simple and widely accessible oral rehydration treatment, small children and the elderly are particularly vulnerable to the extreme dehydration of severe cholera. Case-fatality rates may exceed 20% in affected populations. Globally an estimated 120 000 deaths from cholera occur each year.

Although the establishment of adequate personal hygiene, food safety and sanitation are the mainstay of cholera control, in the short term drastic improvements in these fields are difficult to achieve in most cholera-endemic areas. In the meantime, there is an urgent need for efficient vaccines as an additional public health tool for cholera prevention. A parenteral vaccine based on inactivated *V. cholerae* O1 has been available for more than 40 years. The protective efficacy of this vaccine is modest, of short duration, and it does not prevent transmission of the infective agent. This parenteral vaccine has not for many years been recommended by WHO. New cholera vaccines are under development, and two oral vaccines are already available internationally. One of these vaccines (WC/rBS) consists of killed whole *V. cholerae* O1 cells in combination with a recombinant B subunit of cholera toxin. This killed vaccine is well tolerated and confers high level (85%–90%) protection for six months after the second immunization in all vaccinees older than two years of age. The level of protection is still about 50% three years after immunization in vaccinees who were more than five years of age at the time of vaccination. The other oral vaccine is a live, attenuated vaccine based on the genetically manipulated *V. cholerae* strain CVD103-HgR. A single dose of this live vaccine conferred good protection (60%–100%) in adult volunteers in the United States challenged three months after vaccination, and was also well-tolerated and immunogenic in infants as young as three months of age. This vaccine has not yet proved to provide protection in populations living in disease-endemic areas. However, neither of these oral vaccines has demonstrated sustained protection in children younger than two years of age. Although anti-O139 vaccine candidates are now available, their efficacy is not yet documented.

Compared with the parenteral vaccine, the now internationally available oral vaccines represent significant improvements in terms of protective efficacy, duration of protection, safety and ease of administration.

Cholera vaccination of high-risk populations should be done pre-emptively only, in conjunction with other prevention and control measures. High-risk populations may include, but are not limited to, refugees in crowded camps and residents of urban slums.

For vaccination of populations at immediate risk of a cholera epidemic ("immediate" is defined as a risk that is likely to occur within a period of up to six months), the WC/rBS vaccine is currently recommended by WHO. In cholera outbreak situations where logistical constraints preclude a 2-dose immunization regimen, the use of single-dose CVD 103-HgR may be recommended once its efficacy has been demonstrated in disease-endemic areas.

For immunization of travellers to areas of high endemicity, either of the two oral vaccines may be used, keeping in mind that protection is obtained seven days after the single-dose vaccination with CVD 103-HgR and seven days after the second vaccination with the WC/rBS vaccine.

There is an urgent need for cholera vaccines that are efficient against the different epidemic types of *V. cholerae*, including the O139 strain, and that confer reliable and long-term protection in all age groups, also among children less than five years of age.

Public health impact

Throughout history, devastating outbreaks of cholera have resulted in millions of cases and hundreds of thousands of deaths. Altogether seven cholera pandemics have been recorded. The latest one, which is still ongoing, started in Indonesia in 1961, reached the African continent in the 1970s and South America in 1991. By 1994, over 1 million cases and nearly 10 000 deaths had been reported on the American continent. In part owing to surveillance difficulties, but also for fear of economic and societal consequences, the morbidity and mortality caused by *V. cholerae* are likely to be grossly underreported. Globally, an estimated 120 000 deaths are caused by cholera each year. With proper treatment, the case-fatality rate (CFR) should not exceed 1%, but occasionally levels as high as 40% have been reported. During 1996 and 1997, the outbreak in the Americas seemed to decline, but cumulative figures from 1998 again showed an increase, especially in Peru, where the incidence increased from 3500 to 41 700. In 1999, the reported incidence in South America declined by 86%. On a global basis, from 1997 to 1998 an increase from less than 140 000 cases to more than 290 000 was reported. In 1999, global incidence was about 254 000, and Africa alone accounted for about 81% of the total global number of cases. The same year CFR in Africa reached 4.2%, constituting more than 95% of the world's total deaths from cholera. In 2000, multiple outbreaks of cholera were reported in populations inhabiting various islands in Oceania. As the pandemic is still ongoing, the number of countries affected continues to increase.

Humans are the only known natural host for *V. cholerae,* and the disease is spread by faecal contamination of water and food. Thus cholera endemicity and epidemicity are closely linked to poor sanitation. Direct transmission from person to person is considered to be uncommon. Although oral rehydration may be life-saving, it has no effect on the course of the disease or dissemination of the infection.

The economic impact of cholera in terms of reduced production, failing food exports and decreased tourism can be significant. In Peru, during the cholera outbreak in the early 1990s, the losses were estimated at several hundred million dollars in one year only. Such serious economic consequences contribute to the common underreporting of cholera cases.

The pathogen and the disease

V. cholerae is a Gram-negative, rod-shaped, mainly waterborne bacterium carrying a single polar flagellum. Serogrouping is based on the polysaccharides of the somatic (O) antigen. Epidemics have almost invariably been caused by *V. cholerae* of the O1 serogroup. Three serotypes (Ogawa, Inaba and Hikojima) and two biotypes of *V. cholerae* (classic and El Tor) are described. The El Tor biotype, originally isolated as an avirulent strain in 1905, has evolved to greater virulence and is responsible for the current pandemic. In 1992, a new serogroup – a genetic derivative of the El Tor biotype – emerged in Bangladesh and caused an extensive epidemic. It has now spread over large parts of Asia and is termed *V. cholerae* O139 "Bengal".

V. cholerae is a non-invasive organism that colonizes the lining epithelium of the gut after penetrating the mucus layer. It affects the small intestine through its secreted choleratoxin (CT) that is composed of five receptor-binding B subunits surrounding one catalytic A subunit. For its toxic action, CT is dependent on a specific receptor, the monosialosyl ganglioside GM_1. Binding of CT increases the intestinal levels of cAMP by increasing the adenylate cyclase activity, and results in secretion of chloride and bicarbonate into the small intestine. As a result, water is drawn from the intravascular and extracellular spaces of the body, and rapidly lost into the gut lumen.

In the majority of cases cholera is characterized by acute, profuse watery diarrhoea of one or a few days' duration. In its extreme manifestation, cholera is one of the most rapidly fatal infectious illnesses known. Within three to four hours of the onset of symptoms, a previously healthy person may become hypotensive and may die within six to eight hours. More commonly, fatal cases progress to shock within 6–12 hours with death following in 18 hours to several days. Blood group O is known to be associated with increased vulnerability to severe cholera (cholera gravis). The diagnosis of cholera is commonly established by isolation of the causative organism from the stools of infected individuals. Agglutination tests with specific antisera are used for diagnostic confirmation.

Mild or moderate dehydration is treated with simple oral rehydration solutions containing salts and glucose. In severe cases, aggressive intravenous rehydration treatment is required. Furthermore, WHO recommends that antibiotics be used in the treatment only of cases of cholera with signs of severe dehydration. Whenever possible the sensitivity of *V. cholerae* to antibiotics should be assessed. Antibiotics are not indicated in the treatment of mild to moderate cholera or for mass prophylaxis. Misguided use of antibiotics has led to the emergence of multiresistant strains, some of which were found to be highly virulent.

Protective immune response

Protective immunity in cholera is mediated mainly, if not exclusively, by antibodies produced locally in the intestinal mucosa and secreted onto the gut mucosal surface. These antibodies are directed against bacterial components including CT, and protect by inhibiting bacterial colonization and multiplication and by blocking toxin action. IgA, IgG and IgM antibodies to cholera antigens have been demonstrated in the intestinal lumen, although in terms of protective immunity intestinal IgA antibodies are the most important ones. Protective antitoxic antibodies in the gut are specific for the B subunit of CT and prevent clinical manifestations by complement independent blocking of toxin binding to epithelial GM_1 ganglioside receptors. Furthermore, growth inhibition may result from antibodies binding to the bacteria and interfering with bacterial motility or with the specific process of bacterial adherence to the epithelium.

Antibodies against several *V. cholerae* antigens including the somatic O antigens are found in the sera of patients recovering from cholera, or as a result of vaccination. Especially the O-group specific antibodies show a complement dependent vibriocidal activity. Peaking 8–10 days after onset of clinical illness, the level of anti-O antibodies decreases to baseline two to seven months later. Although not directly protective, the serum vibriocidal response correlates with resistance to infection.

Following natural infection, the early systemic response to somatic antigens is of the IgM class. Subsequent challenges by either natural or vaccine antigens tend to induce a switch to IgG class antibodies. Circulating anti-CT antibodies may also confer short protection, albeit not at the relatively low level induced by natural infection. Adding the B subunit of CT to an oral vaccine stimulates mucosal formation of intestinal IgA antitoxin and contributes to protection for up to nine months after vaccination. Also, addition of the B subunit results in short-term (three months) cross-protection against diarrhoea caused by enterotoxigenic *Escherichia coli* (ETEC). This produces heat-labile enterotoxin which resembles CT antigenically and pharmacologically. No protection is provided against ETEC strains that produce only heat-stable enterotoxin.

The justification for vaccine control

Cholera is considered to be responsible for at least 120 000 deaths annually. Whereas the aim of effective cholera control is to reduce the CFR to below 1%, in 1997 this figure reached the global average of 4.3%, and in a few African countries rates exceeding 20% were recorded. From 1997 to 1998, the total number of cases reported to WHO doubled, reaching more than 290 000, mainly due to increased epidemic activity in parts of Africa and in Peru. Globally, the number of cases remains high. Apparently, compared to the O1 serogroup, the new strain of *V. cholerae* designated O139 "Bengal" has the same capacity for survival in water. It is still confined to some countries in South and South-East Asia.

Wars and political unrest, climatic changes and natural catastrophes, increased human migration and large numbers of people crowded under poor sanitary conditions have always favoured the spread of epidemics such as cholera. Unfortunately, such conditions are still prevailing in many parts of the world. On the other hand, the 40-year history of the current pandemic shows that in areas of poor hygiene cholera may spread rapidly, even without artificial or natural catastrophes. An increasing number of geographical areas are becoming endemic for cholera, reflecting a failure of socioeconomic infrastructure and difficulties in implementation of control measures. Nearly 120 countries have reported indigenous cases of cholera since 1991; almost half of them have reported cases for at least five out of the past eight years.

Cholera vaccine candidates

(i) Parenteral vaccine

Until recently, the only available cholera vaccines were made from phenol-killed whole cells of *V. cholerae*, administered in two doses, two weeks apart. Unfortunately, the protective efficacy of such vaccines against severe dehydration reaches only about 50%, duration of protection hardly exceeds six months, and they do not prevent transmission of the infectious agent.

WHO requirements for the production and control of the killed whole-cell parenteral cholera vaccines may not be relevant to the production and control of the new generation of cholera vaccines. In addition, such a vaccine is not recommended for general public health use even though it is still produced in some countries. Accordingly, the WHO Expert Committee on Biological Standardization decided to discontinue these requirements in 1999. Currently there is no internationally accepted method for measuring the potencies of the new vaccines that guarantees that they will elicit protective immunity in the target population.

(ii) Oral vaccines

The killed WC/rBS vaccine

A vaccine consisting of killed whole-cell *V. cholerae* O1 in combination with a recombinant B-subunit of cholera toxin (WC/rBS) has been marketed since the early 1990s. Given orally according to a two-dose schedule, this vaccine has been shown to be safe even in pregnancy and during breastfeeding. In a field trial in Bangladesh, three doses of the WC/rBS vaccine resulted in 85% and 50% protection when assessed after six months and three years, respectively, in all age groups including children of less than five years of age. Protection in children two to five years of age declined rapidly after the first six months of follow-up, and disappeared entirely during the third year after vaccination. In a more recent field trial in Peru involving military recruits, two doses of the WC/rBS vaccine given one to two weeks apart induced initial protection in 86% of the vaccinees. Importantly, the latter results were achieved in a previously unexposed population of individuals who were almost exclusively of blood group O. On average, the vaccine confers 50%–60% protection for at least three years. Based on dose-response studies, the recommended schedule is now two doses, 10–14 days apart.

During the first three months following vaccination, WC/rBS is about 60% efficacious against enterotoxigenic *E. coli* (ETEC), and in 1995 the indication for its use was extended to ETEC. Data are not available on WC/rBS immunization simultaneously with other vaccines. There is, however, no theoretical risk prohibiting simultaneous administration.

The only reported adverse effect of WC/rBS vaccination is occasional mild gastrointestinal disturbance. Except for possible hypersensitivity to any of the components, no contraindications are known for this vaccine. It is well tolerated by HIV-positive individuals. WC/rBS is currently licensed in Argentina, Guatemala, El Salvador, Estonia, Honduras, Madagascar, Nicaragua, Norway, Peru and Sweden.

By technology transfer, a simplified version of the killed whole-cell vaccine (without the B-subunit) has been locally produced, tested and licensed in Viet Nam. Two oral doses resulted in 66% protective efficacy during a local cholera outbreak that occurred 8–10 months after vaccination. Importantly, among children aged one to five years, the protective efficacy was 68% during the same outbreak. Since 1997, in an area of Viet Nam endemic for cholera, a second-generation bivalent vaccine, containing the serogroup O139 in addition to O1, is being tested in a large-scale randomized, double-blind, placebo-controlled effectiveness trial.

The live, attenuated CVD 103-HgR vaccine

A live, attenuated oral cholera vaccine containing the genetically manipulated classical *V. cholerae* strain CVD 103-HgR has been available since 1994. Extensive trials in a number of countries in Africa, Asia and Latin America have established the safety and immunogenicity of this single-dose vaccine, even in HIV-infected individuals. Experimental challenge studies in volunteers demonstrated protection as early as one week after vaccination. A high level of protection (more than 90%) was conferred against moderate and severe cholera caused by challenge with *V. cholerae* O1 of either El Tor or classical biotype. The overall protective effect against El Tor cholera of any severity (i.e. including mild cases) was 80%.

As with the WC/rBS vaccine, individuals of blood group O seroconverted at the same rate as did other vaccinees. However, in some clinical trials with CVD 103-HgR the geometric mean titre among subjects of blood group O was significantly higher than the corresponding level of non-O individuals. Protection lasts for at least six months; data beyond that time are not available so far.

In a randomized placebo-controlled field trial in Indonesia a single dose of CVD 103-HgR conferred no statistically significant protection during the first six months after vaccination, and only 18% protection during the first year. The very low numbers of cases encountered during the first year (compared to the number expected in the trial area) make the estimates of protection imprecise. The single dose of CVD 103-HgR did not confer significant long-term protection during the four years of observation.

It is not yet established whether this vaccine confers any protection in children below two years of age, although it has been shown to be well-tolerated and immunogenic in infants as young as three months of age. Like the WC/rBS vaccine, CVD 103-HgR would not be expected to confer protection against *V. cholerae* O139.

When CVD 103-HgR was given in combination with the live, oral typhoid vaccine Ty21a, no mutual interference was observed.

Except for transient mild diarrhoea in about 2% of the vaccines, single cases of nausea and abdominal cramps, adverse reactions to the vaccine are not reported. There are no contraindications for the use of CVD 103-HgR other than possible hypersensitivity to any of its components.

Since controlled studies have not been conducted with pregnant women, they should be immunized with the CVD 103-HgR vaccine only if there is a high risk of contracting cholera and if no adequate therapy or inactivated cholera vaccine is available. The vaccine is currently licensed in Argentina, Canada, Colombia, Finland, Guatemala, Peru, the Philippines, Sri Lanka, Switzerland and Venezuela.

WHO position on cholera vaccines

Both the WC/rBS and CVD 103-HgR vaccines have proved to be safe and without significant adverse effects. Compared to the old parenteral vaccine, the more recent oral vaccines provide better and more long-lasting protection against cholera. However, insufficient protection in children below two years of age excludes these vaccines from use in national infant immunization services.

The main indication for vaccination against cholera is protection of the population at risk in disease-endemic areas. For cost-effectiveness reasons, cholera vaccine should be considered only for pre-emptive use, not reactively as a method of containing an outbreak once it has started. Vaccination to prevent cholera outbreaks should be undertaken only in concert with other prevention and control measures currently recommended by WHO. In emergency situations, high-risk populations such as refugees in primitive camps and urban slum residents should be immunized.

Intervention studies should be performed to establish the role cholera vaccination can play in cholera control programmes. Owing to its low efficacy and short duration of protection, use of the old parenteral vaccine is not recommended.

Among the new-generation cholera vaccines, convincing protection in field situations has been demonstrated only with the WC/rBS vaccine. Thus, the WC/rBS vaccine should be considered in populations believed to be at imminent risk of a cholera epidemic. Nevertheless, there are instances where during the disruption caused by epidemic cholera, the logistics of administering two doses separated by more than one week may be difficult to achieve. In such instances, the use of CVD 103-HgR may be recommended once its efficacy has been demonstrated in disease-endemic areas.

Both the WC/rBS and the CVD 103-HgR vaccines may be recommended for travellers to high-risk regions. When rapid protection is important, the CVD 103-HgR vaccine should be preferred as it already induces protection seven days after a single dose. The WC/rBS vaccine is given in two doses separated by at least one week, and protection is obtained one week after the second dose.

The currently available oral vaccines against cholera represent encouraging developments, but further improvements are mandatory in order to protect those in greatest need against the full range of epidemic *V. cholerae* strains.

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Administration summary

Type of vaccine	Killed and live attenuated
Number of doses	Two, 10–14 days apart (oral killed vaccine); one (oral live vaccine)
Schedule	As circumstances dictate for high-risk groups
Booster	None
Contraindications	Hypersensitivity to previous dose
Adverse reactions	Mild local and systemic reactions
Special precautions	No antibiotics from one week before until one week after vaccine (live vaccine) Avoid proguanil from one week before to one week after vaccination (live vaccine) Strict precautions regarding food, water and hygiene

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Diphtheria toxoid vaccine

Public health strategies

Diphtheria is a bacterial infection caused by *Corynebacterium diphtheriae*, transmitted from person to person through close physical and respiratory contact. It can cause infection of the nasopharynx, which may lead to breathing difficulties and death. It was a cyclical epidemic disease but, with rising immunization levels in all countries, epidemics gave way to sporadic cases and intermittent outbreaks of low intensity. This change occurred in the 1940s and 1950s in most industrialized countries, coinciding with an increased use of DTP. No longer was diphtheria thought of as a child killer. Tropical countries are more likely to experience cases of skin infection than the outbreaks of diphtheria which, in cooler climates, tend to be nasopharyngeal infection.

Recent large epidemics of diphtheria in several countries of Eastern Europe again called attention to this disease. They highlighted the need for the following five major activities in diphtheria control:

- adequate surveillance;
- high levels of routine immunization in appropriate age groups;
- prompt recognition, appropriate case management and the availability of adequate supplies of antibiotics and antitoxin;
- rapid case investigation and management of close contacts;
- outbreak management.

WHO perspective

The priority for every country is to reach at least 90% coverage with three primary doses of DTP as early as possible in the schedule. DTP is the core vaccine in childhood immunization services. Since 1990 the global coverage for this triple vaccine has only been around 80%.

Where resources permit, additional doses of DTP should be given after completion of the primary doses. However, the need and timing for such additional booster doses should be addressed by individual national programmes.

In countries where pertussis is no longer a public health problem, bivalent vaccine in its paediatric form (DT) may be used for booster doses in preschool children. The adult form (Td) should be used for booster doses in children aged seven years and over and in adolescents and adults. The following three DTP immunization schedules are in widespread use:

- three doses: three primary doses of DTP vaccine given during the first year of life;
- four doses: primary series of three doses reinforced with a booster dose usually administered around the second or third year of life;
- five doses: primary series of three doses reinforced with a first booster dose in the second year of life and a second booster given before entering school at the age of four to six years.

Special issues

Vaccine presentation: The triple vaccine is usually used in preschool children for primary and reinforcing immunization, while bivalent vaccine is used for booster doses in preschool children in its paediatric form (DT). From seven years of age onwards, the adult form (Td) is used, containing approximately one-tenth of the amount of diphtheria toxoid that is in the paediatric form. The Td vaccine is used from seven years of age because of the possibility that individuals may have been either subclinically infected by toxigenic *Corynebacterium diphtheriae* or vaccinated during infancy, thus making them at increased sensitivity to the diphtheria component. Diphtheria toxoid is also included in the pentavalent DTP–HBV–Hib vaccine.

Outbreaks: The public health burden of diphtheria has been low in most developing countries because most children have acquired immunity through subclinical or cutaneous infection. Recent outbreaks of diphtheria have been observed in the newly independent States of the former Soviet Union, Algeria, China, Iraq, Jordan, Lao People's Democratic Republic, Lesotho, Mongolia, Sudan, Thailand and the Yemen Arab Republic, showing the importance of immunizing children in all countries. These recent outbreaks among adults show the need, still incompletely met in many countries, to maintain immunity against the disease throughout life.

Booster doses: Booster doses may be needed to maintain immunity. Some industrialized countries recommend boosters every 10 years.

Administration summary

Type of vaccine	Toxoid as DTP, DT or Td
Number of doses	At least three primary doses given by the intramuscular route
Schedule	6, 10, 14 weeks of age*
Booster	DTP at 18 months to 4 years of age;** Td every 10 years
Contraindications	Anaphylactic reaction to previous dose
Adverse reactions	Mild local or systemic reactions are common
Special precautions	Reduced diphtheria (Td instead of DT) content from seven years of age

* There is considerable variation in the timing of the three primary doses between different national immunization schedules.

** WHO recommends that, where resources permit, an additional dose of DTP be given approximately one year after completion of the primary doses. However, the need for additional booster doses of DTP, DT or Td should be addressed by individual national programmes.

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Haemophilus influenzae type b vaccine

Summary and conclusions

Wherever thorough studies have been performed, *Haemophilus influenzae* type b (Hib) has been shown to be an important cause of childhood meningitis and a major cause of bacterial pneumonia in children. Although little population-based incidence data are available from most of Asia and the newly independent States of the former Soviet Union, Hib is estimated to cause at least 3 million cases of serious disease and hundreds of thousands of deaths annually, worldwide. The most important manifestations of Hib disease, namely pneumonia and meningitis, are seen mainly in children under five years of age, particularly infants. Currently, several different Hib vaccines, all conjugate vaccines, are on the market. These vaccines have shown protective efficacy in early infancy. Hib vaccines are now used as part of routine childhood vaccination programmes in more than 20 countries including Australia, Canada, New Zealand, the United States, and many countries of western Europe, and have proved to be highly efficacious and virtually free from serious side-effects. Also, excellent results of trials or national introduction in Chile, Uruguay, and the Gambia show that Hib conjugate vaccines are effective in developing country settings. Because these vaccines significantly reduce nasopharyngeal carriage, a herd effect is achieved through Hib vaccination.

In view of the demonstrated safety and efficacy of the Hib conjugate vaccines, Hib vaccine should be included, as appropriate to national capacities and priorities, in routine infant immunization services. In geographical regions where the burden of Hib disease is unclear, efforts should be made to evaluate the magnitude of the problem.

Public health impact

H. influenzae type b (Hib) is estimated to cause at least 3 million cases of serious disease and 400 000–700 000 deaths each year in young children. Rarely occurring in infants under three months, and after the age of six years, the disease burden is highest at 4–18 months of age. In both developed and developing countries Hib is the dominant cause of non-epidemic bacterial meningitis in this age group, and is frequently associated with severe neurological sequelae despite prompt and adequate antibiotic treatment. In economically developed countries meningitis accounts for the majority of invasive Hib disease, whereas in developing countries acute respiratory infection, particularly the estimated 2–3 million cases of Hib pneumonia occurring each year, represents an even heavier disease burden. Other important, but less frequent, manifestations of Hib disease include epiglottitis, osteomyelitis, septic arthritis, and septicaemia.

Following introduction of Hib conjugate vaccines into routine childhood immunization services in the 1990s, Hib disease has largely disappeared in Australia, Canada, New Zealand, the United States and Western Europe.

The pathogen

H. influenzae is a Gram-negative bacterium. Serious infection is usually caused by strains carrying a polysaccharide capsule. Of the six capsular types, type b (Hib) causes almost all systemic infections. This polysaccharide is a polymer of D-ribose-ribitol-phosphate (PRP) and is an essential virulence factor. Up to 15% of children in non-immunized populations may harbour Hib in their nasopharynx. However, only a fraction of those acquiring the microorganism will subsequently develop clinical disease. Transmission of Hib is by droplets originating from colonized persons and hence, asymptomatic carriers are important disseminators of the organism. The non-encapsulated strains that are more frequently isolated from naso-pharyngeal secretions are mainly associated with mucosal infections such as bronchitis and otitis.

Facilities for reliable cultivation of Hib and identification of the capsular polysaccharide by immunological techniques are found in laboratories well-equipped for clinical microbiology, but are not easily available throughout the world.

Immune response

In older children and adults the Hib polysaccharide induces production of bactericidal antibodies. However, this polysaccharide does not reliably elicit protective levels of antibodies in children less than 18 months of age. Furthermore, it does not induce immunological memory and consequently no booster response with subsequent exposure to the polysaccharide. For these reasons, a new generation of vaccines was developed by conjugating a T-cell dependent protein antigen to the Hib polysaccharide. These Hib conjugate vaccines not only induce protective circulating antibodies and immunological memory in infants, but also result in decreased nasopharyngeal colonization of Hib. Thus, a herd effect is achieved through reduced transmission of the microorganism.

Justification for vaccine control of Hib disease

Hib disease, mainly meningitis and pneumonia in young children, is a significant public health concern in both developed and developing countries. In developed countries meningitis is the most important manifestation, whereas in developing countries pneumonia is more common. However, due to inherent problems regarding etiological diagnosis, especially of pneumonia, the true burden of Hib may be seen only by a reduction in the incidence of pneumonia and meningitis following vaccination. Antibiotics are essential for treatment, but have only a minor role in control, and development of bacterial resistance to some of the most efficient antibiotics underlines the need for prevention. Vaccines are the only public health tool available to prevent the vast majority of Hib disease.

The safety, efficacy and effectiveness of the Hib conjugate vaccines are clearly demonstrated in developed countries, where rapid declines in disease incidence have been documented in every country in which the vaccine has been used routinely in childhood immunization services. Furthermore, several studies demonstrate high efficacy of the vaccines against invasive disease in high-incidence and developing country settings, including studies in Chile, in the Gambia and in a Native American population in the United States. In the Gambian trial, vaccinated infants were protected against laboratory-confirmed Hib pneumonia, and the incidence of all X-ray documented pneumonia was reduced by approximately 20%.

A series of cost-benefit analyses in industrialized countries underscores the value of routine immunization against Hib disease. Substantially more disease could be prevented in the developing world, where the burden of disease and death is many times higher. An assessment of the situation in representative countries of most geographical regions was recently made by the Children's Vaccine Initiative. This study showed that inclusion of Hib vaccine into the respective childhood immunization schedules may be cost-effective, even in the lowest income strata.

Haemophilus influenzae type b conjugate vaccines (Hib-vaccines)

The vaccines currently licensed for use against Hib disease are based on Hib-polysaccharide conjugated to a protein carrier, such as diphtheria toxoid (PRP-D), a diphtheria toxoid-like protein (PRP-HbOC), tetanus toxoid (PRP-T), or meningococcal outer membrane protein (PRP-OMP). The conjugation of PRP to the protein induces a T-cell dependent immune response to the Hib-polysaccharide. The conjugate vaccines differ in their carrier protein, method of chemical conjugation and by polysaccharide size, giving them somewhat different immunological properties.

The vaccine is usually given in infancy as repeated doses together with diphtheria/tetanus/pertussis (DTP) and other vaccines of the national childhood immunization services. A booster dose is recommended in most countries at 12–18 months of age, but may not be necessary, especially in developing countries where most of the Hib disease occurs before this age. In adults and children over 18 months of age a single dose is sufficient to induce immunity.

All conjugate Hib vaccines are given by the intramuscular route. No serious side-effects are recorded, and no contraindications known, except for hypersensitivity to the vaccine components. The Hib vaccine may safely be administered concurrently with any vaccine of the EPI or corresponding national childhood vaccination programmes, as well as with pneumococcal and meningococcal vaccines.

WHO position on Hib vaccines

The commercially available Hib conjugate vaccines are all of known good quality. The indication for the use of these vaccines is protection of children below five years of age, particularly infants. WHO encourages the introduction of Hib vaccines worldwide. However, because of differences in epidemiology, health priorities and economic capacity, Hib vaccines will in practice be introduced at different speeds into national immunization services. The emphasis is on introduction in countries with the highest disease burden.

The efficacy and effectiveness of the Hib conjugate vaccines have been clearly demonstrated in developed countries, where rapid declines in disease incidence have been documented in every country in which the vaccine has been used routinely. Several studies also demonstrate the efficacy in high-incidence and developing-country settings.

Three out of the four currently-licensed Hib conjugate vaccines (PRP-HbOC, PRP-OMP, PRP-T) have proven to be comparably efficacious in infancy, provided a complete primary series is given. Furthermore, these vaccines are easily adapted to the routine schedule of the national immunization services. One of the vaccines (PRP-D) performs less well in children below 18 months of age, and is therefore not licensed for use in infants in many countries. All conjugate vaccines have an excellent safety record, and, where tested, do not interfere substantially with the immunogenicity of simultaneously given vaccines.

Unfortunately, in large areas of Asia as well as in the Newly Independent States, population-based data on the burden of Hib disease are largely missing, and so far, few Asian countries have adopted Hib vaccine as part of their routine immunization service. Data from additional surveillance studies are needed to assist public health planners in these areas. A WHO-sponsored protocol to evaluate Hib disease burden is available on request. However, the lack of simple, rapid and reliable techniques for etiological diagnosis of pneumonia is a challenge to future research.

Other issues which must be faced as the vaccine is introduced into developing countries include combination with other antigens such as locally produced DTP, and conceivably with pneumococcal and/or meningococcal vaccines. Also, questions of appropriate formulation including multidose vials, and liquid versus lyophilized vaccine preparations, will have to be addressed.

This chapter was last published as a WHO position paper: The WHO position paper on *Haemophilus influenzae* type b conjugate vaccines. *Weekly Epidemiological Record*, 1998, 73:64–68. It is also available on the Internet http://www.who.int/wer/pdf/1998/wer7310.pdf.

Administration summary

Type of vaccine	Conjugate
Number of doses	Two or three doses in the primary series (depending on manufacturer)
Schedule	6, 10, 14 weeks of age for three doses of primary series (depending on manufacturer)
Booster	None
Contraindications	Hypersensitivity to previous dose
Adverse reactions	Mild local reaction
Special precautions	None

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Hepatitis A vaccine

Summary and conclusion

Hepatitis A is an acute, usually self-limiting disease of the liver caused by hepatitis A virus (HAV). HAV is transmitted from person to person, primarily by the faecal-oral route. The incidence of hepatitis A is closely related to socioeconomic development, and sero-epidemiological studies show that prevalence of anti-HAV antibodies in the general population varies from 15% to close to 100% in different parts of the world. An estimated 1.5 million clinical cases of hepatitis A occur each year. In young children HAV infection is usually asymptomatic whereas symptomatic disease occurs more commonly among adults. Infection with HAV induces lifelong immunity. In areas of low endemicity, hepatitis A usually occurs as single cases among persons in high-risk groups or as outbreaks involving a small number of persons. In areas of high endemicity most persons are infected with HAV without symptoms during childhood. In countries of low and intermediate disease endemicity, adult disease is seen more often and hepatitis A may represent a substantial medical and economic burden. Currently, four inactivated vaccines against HAV are internationally available. All four vaccines are safe and effective, with long-lasting protection. None of the vaccines are licensed for children less than one year of age.

The results of appropriate epidemiological and cost-benefit studies should be carefully considered before deciding on national policies concerning immunization against hepatitis A. As part of this decision process, the public health impact of hepatitis A should be weighed against the impact of other vaccine-preventable infections, including diseases caused by hepatitis B, *Haemophilus influenzae* type b, rubella and yellow fever.

In countries highly endemic for hepatitis A, almost all persons are infected in childhood with the virus without showing symptoms, effectively preventing clinical hepatitis A in adolescents and adults. In these countries, large-scale vaccination programmes are not recommended. In countries of intermediate disease endemicity, where a relatively large proportion of the adult population is susceptible to HAV, and where hepatitis A represents a significant public health burden, large-scale childhood vaccination may be considered as a supplement to health education and improved sanitation.

In regions of low disease endemicity, vaccination against hepatitis A is indicated for individuals with increased risk of contracting the infection, such as travellers to areas of intermediate or high endemicity.

Public health impact

Hepatitis A is an acute, usually self-limiting infection of the liver caused by hepatitis A virus (HAV). The virus has a worldwide distribution and causes about 1.5 million cases of clinical hepatitis each year. Humans are the only reservoir of the organism. Transmission occurs primarily through the faecal-oral route, and is closely associated with poor sanitary conditions. The most common modes of transmission include close personal contact with an infected person and ingestion of contaminated food and water. The virus is shed in the faeces of persons with both asymptomatic and symptomatic infection. Under favourable conditions HAV may survive in the environment for months. Bloodborne transmission of HAV occurs, but is much less common.

The average incubation period is 28 days, but may vary from 15–50 days. Approximately 10–12 days after infection the virus can be detected in blood and faeces. In general, a person is most infectious from 14–21 days before the onset of symptoms, through to 7 days after the onset of symptoms.

Antibodies against HAV develop in response to infection and seroprevalence can be used as a marker of viral transmission in a community. The lowest seroprevalence is found in the Nordic countries (about 15%). In Australia, other parts of Europe, Japan and in the United States, 40%–70% of the adult population has demonstrable antibodies to HAV. Practically all adults living in developing areas of the world have serological evidence of past infection.

The risk of developing symptomatic illness following HAV infection is directly correlated to age. In children below six years of age, HAV infection is usually asymptomatic, with only 10% developing jaundice. Among older children and adults, infection usually causes clinical disease, with jaundice occurring in more than 70% of cases. Therefore, highly HAV-endemic regions are characterized by asymptomatic childhood infection, with only the occasional occurrence of clinical hepatitis A.

For practical purposes, the world can be divided into areas of low, intermediate and high disease endemicity, although there may be regional differences in endemicity within a country. In areas of low endemicity the disease occurs mainly in adolescents and adults in high-risk groups (e.g. homosexual men, injecting-drug users), persons travelling to countries of intermediate and high HAV endemicity, and in certain subpopulations (e.g. closed religious communities). Some of these groups may also experience periodic outbreaks of hepatitis A. In areas of low endemicity, occasional food and waterborne outbreaks of hepatitis A occur. In areas of intermediate endemicity, transmission occurs primarily from person to person in the general community, often with periodic outbreaks. In these countries many individuals escape early childhood infection, but are exposed later in life when clinical hepatitis occurs more frequently. In these areas, most cases occur in late childhood and early adulthood.

In areas of high disease endemicity, where the lifetime risk of infection is greater than 90%, most infections occur in early childhood and are asymptomatic. Thus, clinically apparent hepatitis A is rarely seen in these countries. Countries in transition from developing to developed economies will gradually move from high to intermediate endemicity, and hepatitis A is likely to become a more serious problem in these areas.

Although hepatitis A is mostly self-limiting and rarely fatal, the disease may represent a substantial economic burden, particularly in countries with low and intermediate incidence rates. In the United States, a region of relatively low hepatitis A endemicity, calculations based on surveillance data from 1989 indicated annual medical and work-loss costs of approximately US$ 200 million.

The pathogen and the disease

HAV is a member of the *Picornaviridae* family that includes both the enteroviruses and rhinoviruses of humans. Being the only species member, it constitutes its own genus named hepatovirus. HAV is a non-enveloped (naked) virus of 27–28 nm diameter without morphological features differentiating it from other picornaviruses. Four structural proteins encapsulate the RNA genome. Neutralization sites for anti-HAV antibodies are mainly contained in two of these proteins. Although six genotypes of HAV have been identified, there appears to be no variation detectable by serology in these neutralization sites. The virus is relatively stable at low pH and moderate temperatures, but is inactivated by high temperature (almost instantly at 85°C/185°F), and by formalin or chlorine. HAV itself is not cytopathic and the liver-cell damage is caused by the cell-mediated immune response.

The clinical course of acute hepatitis A is indistinguishable from other types of acute viral hepatitis. Symptoms typically include fever, malaise, anorexia, nausea and abdominal discomfort, followed by dark urine and jaundice. The severity of disease and mortality increases in older age groups. The convalescence following hepatitis A may be slow, and is characterized by fatigue, nausea and lack of appetite. Complications of hepatitis A include relapsing hepatitis, cholestatic hepatitis and fulminant hepatitis. Fulminant hepatitis occurs in approximately 0.01% of clinical infections and is characterized by rapid deterioration in liver function and a very high fatality rate. Chronic infection with HAV does not occur. No specific antiviral therapy is currently available.

The aetiological diagnosis is made by the demonstration of IgM antibodies to HAV (IgM anti-HAV) in serum. Detection of the virus or viral antigens in the stool is of limited value for routine diagnosis.

Protective immune response

Protective antibodies develop in response to infection and persist for life. The protective role of anti-HAV antibodies has been demonstrated by the protection against hepatitis A resulting from passive immunization with serum immune globulin. The effect of mucosal immunity on HAV infection is not known.

Justification for vaccine control

Although usually a self-limiting disease without serious sequelae and with a low case-fatality rate, human suffering may, as a result of infection, be considerable. In addition, direct and indirect medical costs including the infection control measures involved, may impose a considerable economic burden on society. Cost-benefit analyses from the United States suggest that large-scale immunization services might

result in cost savings in some communities. However, depending on the costs associated with clinical disease and vaccination (vaccine and administration), such cost-benefit figures will vary considerably between different countries.

In the long term, socioeconomic development will reduce transmission of hepatitis A, particularly through improved sanitation and health education. Unfortunately, in some parts of the world socioeconomic development is slow. No drugs against HAV are currently available, and antiviral medication is unlikely to become a realistic alternative to appropriate vaccines. Immune globulin may be used for pre- and post-exposure prophylaxis, for example, shortly before entering a disease-endemic area or just after likely HAV exposure. However, passive immunization with immune globulin gives only short-term protection (three to five months) and is relatively costly compared to the long-term immunity from vaccination.

Several vaccines against hepatitis A are now available that are highly efficacious and provide long-lasting protection in adults and in children above one to two years of age. In countries where clinical hepatitis A is an important health problem, immunization is likely to be a cost-effective public health tool to control the disease.

Hepatitis A vaccines

Techniques for growing HAV in cell culture have made it possible to generate sufficient amounts of virus for vaccine production. Several inactivated or live attenuated vaccines against hepatitis A have been developed, but only four inactivated hepatitis A vaccines are currently available internationally. All four vaccines are similar in terms of efficacy and side-effect profile. The vaccines are given parenterally, as a two-dose series, 6-18 months apart. The dose of vaccine, vaccination schedule, ages for which the vaccine is licensed, and whether there is a paediatric and adult formulation varies from manufacturer to manufacturer. No vaccine is licensed for children younger than one year of age.

Three vaccines are manufactured from cell-culture-adapted HAV propagated in human fibroblasts. Following purification from cell lysates, the HAV preparation is formalin-inactivated and adsorbed to an aluminium hydroxide adjuvant. One vaccine is formulated without preservative; the other two are prepared with 2-phenoxyethanol as a preservative. The fourth vaccine is manufactured from HAV purified from infected human diploid cell cultures and inactivated with formalin. This preparation is adsorbed to biodegradable, 150 nm phospholipid vesicles spiked with influenza haemagglutinin and neuramidase. These virosomes are thought to directly target influenza-primed antibody-presenting cells as well as macrophages, thus stimulating a rapid vaccine-induced B-cell and T-cell proliferation in the majority of vaccinees. A combination vaccine containing inactivated hepatitis A and recombinant hepatitis B vaccines has been licensed since 1996 for use in children aged one year or older in several countries. The combination vaccine is given as a three-dose series, using a 0, 1, 6 month schedule.

Hepatitis A vaccines are all highly immunogenic. Nearly 100% of adults will develop protective levels of antibody within one month after a single dose of vaccine. Similar results are obtained with children and adolescents in both developing and developed countries. The protective efficacy of the vaccine against clinical disease

was determined in two large trials. Among almost 40 000 Thai children aged 1–16 years the protective efficacy was 94% (95% confidence intervals: 82%–99%) following two doses of vaccine given one month apart. Among approximately 1000 children aged 2–16 years, living in a highly disease-endemic community in the United States, the efficacy of one dose of vaccine was 100% (95% confidence intervals: 87%–100%).

Although one dose of vaccine provides at least short-term protection, the manufacturers currently recommend two doses to ensure long-term protection. In studies evaluating the duration of protection of two or more doses of hepatitis A vaccine, 99%–100% of vaccinated individuals had levels of antibody indicative of protection five to eight years after vaccination. Kinetic models of antibody decay indicate that the duration of protection is likely to be at least 20 years, and possibly lifelong. Post-marketing surveillance studies are needed to monitor vaccine-induced long-term protection, and to determine the need for booster doses of vaccine. This is especially true in areas of low disease endemicity where natural boosting does not occur.

Millions of persons have now been vaccinated against HAV. The current vaccines are well tolerated and no serious adverse events have been statistically linked to their use. Contraindications to hepatitis A vaccination include a known allergy to any of the vaccine components. Hepatitis A vaccine may be administered with all other vaccines included in the Expanded Programme on Immunization and with vaccines commonly given for travel. Concurrent administration of immune serum globulin does not appear to influence significantly the formation of protective antibodies.

WHO position on hepatitis A vaccines

The currently available vaccines against hepatitis A are all of known good quality and in line with the above WHO recommendations. However, they are not licensed for use in children less than one year of age. The efficacy in children below one year of age is variable owing to interference by passively acquired maternal antibodies. Although the current vaccines result in long-term protection when given as two injections 6–18 months apart, high levels of immunity are obtained after one dose. Studies addressing the duration of protection following a single dose of vaccine are encouraged. Planning for large-scale immunization services against hepatitis A should involve careful analyses of the cost-benefit and sustainability of different appropriate hepatitis A prevention strategies, as well as an assessment of the possible long-term epidemiological implications of vaccination at different levels of coverage.

In countries where hepatitis A is highly endemic, exposure to HAV is almost universal before the age of 10 years. In such countries clinical hepatitis A is usually a minor public health problem, and large-scale immunization efforts against this disease should not be undertaken. In developed countries with low endemicity of hepatitis A and with high rates of disease in specific high-risk populations, vaccination of those populations against hepatitis A may be recommended. The high-risk groups include injection-drug users, homosexual men, persons travelling to high-risk areas, and certain ethnic or religious groups. However, it should be noted that vaccination programmes targeting specific high-risk groups may have little impact on the overall national incidence of disease.

In areas of intermediate endemicity, where transmission occurs primarily from person to person in the general community (often with periodic outbreaks), control of hepatitis A may be achieved through widespread vaccination programmes.

Recommendations for hepatitis A vaccination in outbreak situations depend on the epidemiology of hepatitis A in the community, and the feasibility of rapidly implementing a widespread vaccination programme. The use of hepatitis A vaccine to control community-wide outbreaks has been most successful in small, self-contained communities, when vaccination is started early in the course of the outbreak, and when high coverage of multiple-age cohorts is achieved. Vaccination efforts should be supplemented by health education and improved sanitation.

Although the burden of disease associated with hepatitis A is considerable in many countries, the decision to include hepatitis A vaccine in routine childhood immunization services should be made in the context of the full range of immunization interventions available. This includes hepatitis B, Hib, rubella and yellow fever, and, in the near future, pneumococcal vaccines, all of which are likely to have a more profound public health impact.

This chapter was last published as a WHO position paper: Hepatitis A vaccines: WHO position paper. *Weekly Epidemiological Record,* 2000, 75:38–42 and is available on the Internet at http://www.who.int/wer/pdf/2000/wer7505.pdf.

Administration summary

Type of vaccine*	Inactivated, given by the intramuscular route
Number of doses	Two
Schedule	Second dose 6–18 months after first (timing varies with manufacturer)
Booster	May not be necessary; manufacturers propose at 10 years
Contraindications	Hypersensitivity to previous dose
Adverse reactions	Mild local and systemic reactions
Special precautions	Not protective before one year of age

* A combination vaccine containing inactivated hepatitis A and recombinant hepatitis B vaccine is available for use in children aged one year or older in several countries, and is given as a three-dose series, using a 0, 1, 6 month schedule

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Hepatitis B vaccine

Public health strategies

Hepatitis B is a viral infection of the liver. More than two thousand million people alive today have been infected with the hepatitis B virus. Approximately 350 million are chronically infected and are at high risk of serious illness and death from cirrhosis of the liver and primary liver cancer, diseases that kill 500 000 to 750 000 persons a year. Hepatitis B is preventable with a safe and effective vaccine - the first vaccine against cancer.

The prevalence of chronic hepatitis B virus (HBV) infection is high (more than 8%) in certain areas of the world. These include all of sub-Saharan Africa, South-East Asia, including China, Indonesia, the Democratic People's Republic of Korea, and the Philippines; the Eastern Mediterranean except Israel; South and Western Pacific islands; the interior Amazon Basin; and certain parts of the Caribbean, i.e. the Dominican Republic and Haiti. The disease is moderately prevalent (2%–7%) in South Central and South-West Asia, Israel, Japan, Eastern and Southern Europe, the Russian Federation, and most of Central and South America. In Australia, New Zealand, Northern and Western Europe, and North America, the prevalence of chronic hepatitis B viral infection is low (under 2% of the general population).

If the vaccine is administered before infection, it prevents the development of the disease and the carrier state in almost all individuals. It has been given to more than 500 million persons and has proved one of the safest, most immunogenic and effective vaccines. On a population basis, it is most effective when used routinely as part of the infant immunization schedule, although it can be used in persons of any age.

Dramatic decreases in the cost of the vaccine in developing countries, from US$ 20 to $0.25–0.50 per paediatric dose, have allowed public health officials to consider the mass use of this vaccine in infants. Additionally, an increasing number of countries have recognized the disease burden imposed by chronic HBV infection in terms of chronic liver disease, cirrhosis and liver cancer. These have been important factors in promoting the integration of hepatitis B vaccine into national childhood immunization schedules.

Universal infant immunization is now recognized as the proper strategy for every country for the long-term control of chronic HBV infection and its sequelae (cirrhosis and liver cancer). The vaccine first became available in the United States in 1982 when the initial strategy was to give it as pre-exposure vaccination to populations at high risk for HBV infection (e.g. health care workers, men who have

sex with men, and heterosexual persons with multiple partners). When the vaccine became widely available, a similar strategy was adopted by other industrialized countries. By the mid-1980s, several countries with very high prevalence of chronic HBV infection had begun the routine immunization of infants at birth. In 1992, WHO recommended that hepatitis B vaccine be integrated into national immunization service of all countries with a rate of chronic HBV infection of 8% or higher by 1995, and into the programme of all countries by 1997. More than 135 countries have now done so.

WHO perspective

Hepatitis B vaccine should be included in routine childhood immunization schedules for all children in all countries. Some industrialized countries administer the vaccine to adolescents as their primary immunization strategy.

The priorities for hepatitis B immunization strategies in order of importance are:

- routine infant vaccination;
- prevention of perinatal HBV transmission (from mother to baby);
- catch-up vaccination for older age groups.

Routine infant vaccination

The routine vaccination of all infants as an integral part of national immunization schedules should be the highest priority in all countries. In countries of high disease endemicity hepatitis B surface antigen (HBsAg) prevalence (8% or more), routine infant hepatitis B vaccination can rapidly reduce transmission because most chronic infections are acquired as a result of spread either from mother to baby or from child to child in the first year of life. In countries of intermediate hepatitis B viral endemicity (HBsAg prevalence 2%–7%) and low endemicity (HBsAg prevalence below 2%), routine infant hepatitis B vaccination is also the highest priority. This is because a high proportion of chronic infections are acquired during childhood in these countries, and most infections acquired during childhood occur among children born to mothers who are NOT infected with hepatitis B virus. These infections would not be prevented by perinatal hepatitis B prevention services that screen pregnant women for HBsAg and provide post-exposure immunization for infants of HBsAg-positive mothers.

Hepatitis B vaccine schedules are very flexible. There are various options for adding the vaccine to established national immunization schedules without requiring additional visits for vaccination (table 6).

Table 6. Options for adding hepatitis B vaccine to childhood immunization schedules

Age	EPI visit	Antigens given at same visit	No birth dose	With birth dose	
			Option 1	Option 2	Option 3
Birth	0	BCG (OPV0)*		HepB-birth (m)	HepB-birth (m)
6 weeks	1	OPV1, DTP1, Hib1	HepB1(m/c)	HepB2(m)	DTP-HepB1 (c)
10 weeks	2	OPV2, DTP2, Hib2	HepB2(m/c)		DTP-HepB2 (c)
14 weeks	3	OPV3, DTP3, Hib3	HepB3(m/c)	HepB3(m)	DTP-HepB3 (c)
9–12 months	4	Measles	Measles	Measles	Measles

* Only given in countries of high disease endemicity
(m) = monovalent vaccine (m/c) = monovalent or combination vaccine (c) = combination vaccine

Programmatically, it is usually easiest if the three doses of hepatitis B vaccine are given at the same time as the three doses of DTP (table 6, option I). This schedule prevents infections acquired during early childhood, which account for most of the disease burden related to hepatitis B virus in countries of high disease endemicity, and also prevents infections acquired later in life. However, this schedule does not prevent perinatal hepatitis B virus infections because it does not include a dose of hepatitis B vaccine at birth.

Other schedule options can be used to prevent perinatal hepatitis B virus infections: a three-dose schedule of monovalent hepatitis B vaccine, the first dose given at birth and the second and third doses given at the same time as the first and third doses of DTP vaccine (option 2); or a four-dose schedule in which a birth dose of monovalent hepatitis B vaccine is followed by three doses of a combination vaccine (e.g. DTP-HepB) (option 3).

- The three-dose schedule (option 2) is less expensive but is more complicated to administer because infants receive different vaccines at the second EPI visit than at the first and third visits.
- The four-dose schedule (option 3) is easier to administer programmatically but is more costly.

Prevention of perinatal hepatitis B virus transmission

In order to prevent hepatitis B virus transmission from mother to baby the first dose of hepatitis B vaccine needs to be given as soon as possible after birth, preferably within 24 hours. In countries where deliveries take place predominantly in health facilities the most feasible strategy for preventing transmission from mother to baby is to give a dose of hepatitis B vaccine to all infants at birth. An expensive alternative where there is high antenatal attendance is to screen all pregnant women for HBsAg and provide immunization, beginning at birth, to infants of infected mothers. However, extensive resources are required for screening pregnant women and tracking infants of infected mothers.

The priority for the incorporation of strategies aimed at the prevention of perinatal transmission of hepatitis B virus in a particular country should take into account the relative contribution of such transmission to the overall hepatitis B disease burden and the feasibility of delivering the first dose of hepatitis B vaccine at birth. In general it is most feasible to deliver hepatitis B vaccine at birth to infants who are born in health facilities. In addition, the availability of monovalent hepatitis B vaccine in prefilled single-dose injection devices (e.g. Uniject™) can facilitate the administration of hepatitis B vaccine by birth attendants to infants delivered at home.

When considering whether a birth dose should be given the following principles should be taken into account.

- **All countries**

  Achieving a high level of completion of the vaccine series among all infants should be the highest priority and has the greatest overall impact on the prevalence of chronic hepatitis B virus infections in children, regardless of whether it is feasible to administer a birth dose.

- **Countries where a high proportion of chronic HBV infections are acquired perinatally (e.g. in South-East Asia)**

  A birth dose should be given to infants who are delivered in hospitals when hepatitis B vaccine is introduced. Efforts should also be made to give hepatitis B vaccine as soon as possible after birth to infants delivered at home.

- **Countries where a lower proportion of chronic infections is acquired perinatally (e.g. in Africa)**

  The administration of a birth dose may be considered after evaluating the relative contribution of perinatal hepatitis B virus infections to the overall disease burden, and the feasibility and cost-effectiveness of providing such a dose.

Catch-up vaccination for older age groups

When hepatitis B vaccine is incorporated into routine childhood vaccination schedules, over several years the child population will gradually become protected against HBV infection, and the prevalence of chronic HBV infection will decline. The need for catch-up vaccination for older age groups such as adolescents and adults is determined by the baseline epidemiology of HBV infection in the country, the priority given to rapidly reducing the incidence of the disease and considerations of cost-effectiveness. In all countries, health-care workers who are exposed to blood in their work are likely to be at high risk for HBV infection and should be considered for immunization.

In countries of high endemicity (HBsAg prevalence 8% or more) the routine vaccination of infants rapidly reduces the transmission of HBV. In this circumstance, catch-up vaccination of older children is not usually warranted. Catch-up vaccination for older age groups has relatively little impact, since most adults have already been infected.

In countries of intermediate endemicity (HBsAg prevalence 2%–7%) and low endemicity (HBsAg prevalence under 2%) there may be a substantial disease burden attributable to chronic infections acquired by older children, adolescents and adults. Catch-up strategies targeted on these older age groups, in addition to routine infant vaccination, may be considered. Possible target groups for catch-up vaccination include cohorts such as adolescents and persons with risk factors for acquiring hepatitis B viral infection.

Special issues

Booster doses: These are not recommended. Studies have shown that infants, children and adults who have responded to a three-dose hepatitis B immunization series are protected from hepatitis B for at least 15 years even if they lose detectable antibodies over time. Long-term protection relies on the immunological memory, which allows a protective anamnestic antibody response after exposure to HBV.

Public concern: Although concerns have been expressed over the past 20 years that certain chronic illnesses might be caused by hepatitis B vaccine, no evidence exists that any of these diseases are caused by the vaccine. For example, in the mid-1990s, concern was expressed that the vaccine might cause multiple sclerosis. However, studies do not support this, and a report in 2002 by the United States Institute of Medicine found no evidence of a causal relationship between hepatitis B vaccination in adults and multiple sclerosis.

Administration summary

Type of vaccine	Recombinant DNA or plasma-derived
Number of doses	Three doses given by the intramuscular route into upper thigh of infant and deltoid muscle of adult
Schedule	Several options (see above)
Booster	None
Contraindications	Anaphylactic reaction to a previous dose
Adverse reactions	Local soreness and redness, rarely anaphylactic reaction
Special precautions	Birth dose must be given if there is a risk of perinatal transmission

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Influenza vaccine

Summary and conclusions

Influenza virus types A and B are both common causes of acute respiratory illnesses. Although both virus types may cause epidemics of considerable morbidity and mortality, influenza B infections are often limited to localized outbreaks; whereas influenza A viruses are the principal cause of larger epidemics including worldwide pandemics. In temperate regions, influenza occurs in winter epidemics that affect 1%–5% of the population. In tropical regions, influenza can be contracted throughout the year and its contribution to overall morbidity and mortality is less well defined.

Rates of infection are highest in children, but severe morbidity and mortality from the disease are more common among the elderly and in specific high-risk groups. In many developing countries, knowledge concerning the local epidemiology of influenza is fragmentary or non-existent. The total economic impact of an influenza epidemic is considerable, and in industrialized countries total estimated costs (direct and indirect) may reach approximately US$ 10–60 million per million population.

Influenza A viruses undergo frequent changes in their surface antigens, whereas type B influenza viruses change less frequently. Immunity following infection by one strain may not protect fully against subsequent antigenic variants. As a consequence, new vaccines against influenza must be designed each year to match the circulating strains that are most likely to cause the next epidemic. To this end, WHO has established a Global Influenza Surveillance Network, the results of which form the foundation for WHO's annual recommendations on the influenza vaccine composition. Currently, two subtypes of influenza A (A/H1N1 and A/H3N2) virus as well as influenza B virus are included in the vaccine. Among healthy adults, appropriate influenza vaccines will in general achieve protection rates of about 50%–80% against clinical disease, whereas vaccination of the elderly reduces the risk of serious complications or death by 70%–85%.

Public health impact

Both influenza A and B are important causes of acute respiratory illness. Although influenza B virus is often associated with limited outbreaks of relatively mild disease, it may occasionally cause severe epidemics with considerable mortality rates. However, due to frequent changes in the antigens constituting the viral subtype, influenza A is the principal cause of widespread epidemics of high mortality and of influenza pandemics. Immunity induced by one subtype of influenza A virus may not protect against variants of the same subtype.

In temperate climates, influenza A epidemics occur almost every year during the winter season. Most epidemics last for three to six weeks, although the virus may be found in the affected communities for several weeks before and after the outbreak. In tropical regions, the virus may cause disease throughout the year, although often displaying a biannual pattern.

Recorded since the middle of the 18th century, major antigenic "shifts" have occurred at intervals averaging 30 years, and resulted in pandemics of which the "Spanish flu" in 1918 was the most severe, probably causing more than 20 million deaths worldwide. Less severe pandemics occurred in 1957, 1968 and 1977.

Influenza occurs in all age groups, with the highest infection rate in children aged five to nine years. However, the highest rates of serious morbidity and of mortality are found among those aged over 65 years. Several medical conditions are known to predispose to complications. These conditions include chronic ailments such as pulmonary or cardiovascular illness, metabolic diseases including diabetes mellitus and renal dysfunction, and various types of immunosuppression. Residents of long-term care facilities are also at high risk of influenza and its complications. Studies in pregnant women suggest increased severity after the first trimester.

Seasonal elevation of mortality above a predicted baseline has long been a measure of the relative severity of influenza epidemics. Since influenza may be confused with other respiratory infections, and its most common complication is pneumonia, the mortality of influenza is often expressed as excess deaths due to pneumonia. During interpandemic periods between 1918–1991, the average annual rate of excess deaths during influenza outbreaks in the United States was 7.5–23 per 100 000 population. The majority of these deaths occurred among individuals over 65 years of age.

In industrialized countries, influenza is associated with a considerable economic burden in terms of health care costs, lost days of work or education and general social disruption. Several studies have estimated costs using a variety of methods. In Germany, the estimated total costs of the 1996–1997 influenza epidemic amounted to approximately US$ 1045 million; in 1989 a French study estimated the total cost of influenza at more than US$ 1900 million. In the United States, the yearly total costs were calculated at US$ 11 000–18 000 million.

WHO has a global virological surveillance programme covering 82 countries and involving more than 100 collaborative laboratories. This network ensures up-to-date antigenic and genetic information on the circulating influenza strains, which is a prerequisite for appropriate formulation of the annual influenza vaccines. Nevertheless, surveillance of influenza varies considerably throughout the world. While seriously limited on the African continent, both virological and disease surveillance is gaining momentum in Asia and South America. The severity of influenza depends in part on the age profile and pre-existing health status of the population. In developing countries, influenza is generally considered less important than several other infectious diseases. This apparently low recognition of influenza as a serious infectious disease is most likely a consequence of the lack of epidemiological data on influenza from many of these regions. Furthermore, where influenza tends to occur all year round and baseline mortality is high,

seasonal excess mortality or illness due to pneumonia is not a reliable measure of its impact. Thus, in many developing countries the importance of influenza can be determined only following well-planned vaccine interventions.

The pathogen and disease

Influenza viruses belong to the family *Orthomyxoviridae* and are separated into types A, B and C according to antigenic differences in their respective nucleocapsid. Only types A and B cause clinical disease of any concern. The segmented, single-stranded RNA genome of these viruses encodes at least 10 proteins.

The viral envelope is composed of a lipid bilayer on a layer of matrix protein (M1). Another important envelope protein, M2, is the target of the antivirals amantadine and rimantadine. Embedded in the lipid bilayer are glycoproteins that possess either haemagglutinin (HA) or neuraminidase (NA) activity. The HA and NA antigens are responsible for virus attachment to and penetration into cells, and release of progency virus from the infected cells respectively, and also determine the subtypes of the influenza A viruses. High mutation rates and frequent genetic reassortments due to the segmental nature of the genome, contribute to great immunological variability, particularly of the HA and NA antigens of influenza A viruses.

Type A viruses are found in animals including pigs, horses and various avian species as well as in man. Viral isolates are described according to type, geographical origin, strain number, year of isolation and subtype, in this order (e.g. A/Sydney/5/97 (H3N2)). Although infrequent exceptions occur, humans are generally infected by viruses of the H1, H2 or H3 and N1 or N2 subtypes. Minor mutations continuously create small changes in these surface glycoproteins, resulting in "antigenic drift". On the other hand, "antigenic shifts" involve major changes caused by reassortment of genetic material from different type A-strains, thought to arise as a result of mixed influenza A infections in animals. However, influenza viruses of animal subtypes may occasionally cause illness in humans directly. Although such viruses are not very efficient in infecting humans, fatality rates may be high. For example, in 1997 an avian H5N1 outbreak occurred in Hong Kong, Special Administrative Region of China. The virus was transmitted from domestic chicken and ducks to humans, resulting in 18 confirmed cases in humans, of which six were fatal. Recently, human-to-human reassortants between A/H3N2 and A/H1N1 have been detected, resulting in the subtype A/H1N2.

Although influenza B virus is mostly associated with lower attack rates and a milder disease, it may occasionally cause epidemics of the same severity as type A viruses. It affects only humans and is primarily a childhood pathogen. Type B viruses do not exhibit the same degree of antigenic variation as does type A.

Influenza virus is spread to susceptible individuals by respiratory secretions, the predominant factor being small-particle aerosols created by an infected person's sneezing, coughing or even talking. Although influenza virus type A is relatively stable under various environmental conditions, survival appears to be favoured by low relative humidity and low temperature.

The incubation time for influenza ranges from one to five days with an average of two days. In most cases, virus is found in specimens from the respiratory tract from one to two days before onset to four to five days after onset of disease, corresponding to the period of communicability. There is no chronic carrier state, but in young children viral shedding tends to last longer than in adults. Clinical onset is characterized by abrupt fever, headache, malaise and myalgias. Systemic symptoms usually last for three days, although occasionally high fever for up to one week is observed. Sore throat, rhinitis and non-productive cough may continue for several days after the systemic symptoms have ceased. Influenza may be misdiagnosed clinically: several infectious agents including respiratory syncytial virus may cause outbreaks of influenza-like disease, illustrating the importance of laboratory-based confirmation of the clinical diagnosis.

Although precise data on influenza-associated deaths are not available for all countries, in the United States influenza-associated deaths range between 30 and 150 per 100 000 population aged over 65 years, and older adults account for more than 90% of deaths attributed to pneumonia and influenza. Secondary bacterial pneumonia (commonly caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Staphylococcus aureus*) is the most frequent complication of influenza and occurs mainly in the elderly and those suffering from certain chronic illnesses. Primary influenza pneumonia is probably an uncommon complication, but has a high fatality rate. Also, croup is significantly associated with influenza outbreaks, albeit at very low rates. Traditionally, the definitive diagnosis of influenza is made either on the basis of virus isolation or by serology. Virus is most frequently isolated from nasopharyngeal or throat swabs, nasal washings or sputum obtained within three days of onset of illness. Cultivation can be done in embryonated hens' eggs, or in cell cultures that support viral replication. Using conventional laboratory tools, at least three to four days are needed for virus demonstration and identification of virus type. Serological confirmation is based on a significant rise in influenza specific IgG and requires that the first serum be taken within five days of onset and the second serum taken at least 10–14 days later. In recent years, rapid tests demonstrating either viral antigens or nucleic acids are becoming increasingly available for the diagnosis of influenza viruses, thus reducing time necessary for virus identification.

Protective immune response

Protection against influenza is thought to be mainly conferred by serum antibodies, although mucosal IgA antibodies and cell-mediated immune responses almost certainly contribute. About one to two weeks after a primary infection neutralizing, haemagglutination inhibiting (HAI) antibodies as well as antibodies to neuraminidase occur in serum, peaking at approximately three to four weeks. After reinfection, the antibody response is more rapid. Influenza antibodies may persist for months or years, although in some high-risk groups antibody levels can begin to decline within a few months after vaccination. The antibodies are specific to variants within a given subtype and protection may be reduced or lost as a consequence of antigenic change in new infecting strains. Presence of HAI titres of 1:40 and greater (or neutralizing titres above 1:8) correlate with immunity. In the elderly, HAI titres higher than 1:80 may be required for protection. Whereas HAI antibodies are involved in protection against infection, antibodies against NA decrease the amount of virus released from infected cells and may ameliorate illness.

Secretory IgA antibodies peak approximately 14 days after infection and can be detected in saliva, nasal secretions, sputum and in tracheal washings. Preceding the occurrence of antibody-producing cells, cytotoxic T lymphocytes with specificity for influenza appear, and serve to limit the infection. Also, mononuclear cells infiltrate infected airways providing antibody dependent cell-mediated cytotoxicity against influenza-infected cells.

The justification for vaccine use

During influenza epidemics, attack rates of 1%–5% are most commonly observed, but the attack rate may reach 40%–50% or more among elderly persons in institutions and in other high-risk groups. At least in western communities, bacterial complications such as pneumonia are frequently associated with influenza; the total annual excess mortality during influenza epidemics is estimated at 7.5–23 per 100 000. Influenza poses a considerable economic burden both on society and the individual in terms of consumption of health care resources and lost productivity.

Internationally-licensed influenza vaccines have proved to be efficacious and safe. During influenza outbreaks, appropriate vaccination may significantly reduce respiratory illness and sick leave among healthy adults. More importantly, vaccination may reduce severe disease and premature death in the elderly and in persons with underlying ailments or disease (*for details on vaccine efficacy, see below*). Antiviral drugs such as the M2 inhibitors (acting against type A virus) and the more recently developed neuraminidase inhibitors (acting against both type A and type B viruses) have been shown to be effective for treatment (and for some agents, prophylaxis) and are now available in many industrialized countries. Resistant mutants to both classes of antiviral agent have been detected, and antimicrobial resistance surveillance is important to assess the magnitude of this problem. Also, costs, occasional side-effects and the likely limited availability of such drugs during major outbreaks highlight the role of vaccination as the primary preventive measure against influenza.

Influenza virus vaccines

Each year in September and February respectively, the WHO Global Influenza Programme recommends the composition of the influenza vaccine for the next season that normally begins in May–June in the southern hemisphere and in November–December in the northern hemisphere. The composition is based on surveillance data from the worldwide network of national influenza centres and WHO collaborating centres. Current available influenza vaccines contain antigens from two A subtypes, H3N2 and H1N1, and one type B virus. These vaccines are of three types:

- whole virus vaccines consisting of inactivated viruses;
- split virus vaccines consisting of virus particles disrupted by detergent treatment;
- sub-unit vaccines consisting essentially of haemagglutinin and neuraminidase from which other virus components have been removed.

Influenza vaccines are normally not adjuvanted. Recently, however, a subunit vaccine containing a novel oil-in-water adjuvant (MF59) was licensed in the European Union. This vaccine seems to achieve enhanced antibody responses in the elderly, although the clinical implications of this finding need further clarification. Live influenza vaccines have been used in the newly independent States of the former Soviet Union and some other countries. Trials with nasal application of live influenza vaccine are currently ongoing in the United States.

The figures for vaccine efficacy vary considerably according to:

1) antigenic match between vaccine and the viral strain causing the outbreak;
2) age group and clinical category of the vaccinees;
3) diagnostic endpoint criteria of the trial; and
4) the accuracy of the diagnosis.

Provided a good antigenic match, inactivated influenza vaccines have been shown to prevent laboratory-confirmed illness in approximately 70%–90% of healthy adult vaccinees. Among the elderly not living in nursing homes, vaccination may reduce the number of hospitalizations by 25%–39% and overall mortality by 39%–75%. Among nursing home residents, influenza vaccination can reduce hospitalizations (all causes) by about 50%, the risk of pneumonia by about 60% and the risk of death (all causes) by 68%.

Most inactivated influenza vaccines are given via the intramuscular route in the deltoid muscle, except in infants where the recommended site is the antero-lateral aspect of the thigh. A single dose of inactivated vaccine annually is appropriate, except for previously unvaccinated preschool children pre-existing with medical conditions who should receive two doses at least one month apart.

The three types of inactivated influenza vaccine show comparable efficacy, but differ in terms of reactogenicity. Thus in 15%–20% of vaccinees, the whole-virus vaccines cause local reactions lasting for one to two days. Such reactions appear to be more common in young children than in adults. Transient systemic reactions such as fever, malaise and myalgias may occur in a minority of vaccine recipients within 6–12 hours of the vaccination. Split vaccines and subunit vaccines show reduced systemic reactogenicity both in children and in adults as compared to whole virus preparations. Consequently, subunit and split virus vaccines are more attractive, particularly for use in children.

In 1976, an association between influenza vaccination and Guillain-Barré syndrome (GBS) was reported in the United States, demonstrating an incidence exceeding the background rate by about 10 cases in 1 million recipients of a vaccine containing swine-influenza-like virus. The annual incidence of GBS is approximately 10–20 cases per million adults. Later studies have not shown a substantial increase in GBS associated with other influenza vaccines, although a slightly elevated risk (representing an excess of 1–2 cases per million vaccinated) was noted following influenza vaccination during the 1992–1993 and 1993–1994 seasons. Even if GBS is truly associated with influenza vaccination, an estimated risk of 1–2 cases per million vaccinated is still far less than the risk of death from influenza and its complications, especially in the target groups of influenza vaccination. Influenza vaccines do not predispose for Reye's syndrome.

A mild, self-limited syndrome of red eyes and one or more of several respiratory symptoms (cough, wheeze, chest tightness, or difficulty breathing) occurring 2–24 hours after vaccination, and resolving within 48 hours, has been described recently in a minority of persons receiving some inactivated influenza vaccines. Studies are currently under way to evaluate the extent of this event, termed the oculo-respiratory syndrome. As the virus used for influenza vaccines is propagated in hens' eggs, influenza vaccine should not be administered to individuals with a definite history of serious allergic reactions to eggs without adequate medical precautions.

Moderate to severe acute illness is a contraindication to influenza vaccination until symptoms have decreased. In spite of the clearly demonstrated advantages of vaccination, in many industrialized countries the uptake of influenza vaccines is suboptimal and is often less than 10% to 20% of high-risk groups. The low vaccine uptake even in high-risk populations may reflect inadequate reimbursement of the vaccine costs as well as a perceived low efficacy and fear of the relatively frequent, albeit mild, side-effects. Also, the fact that influenza is a common disease may lead to misperception of the burden it imposes on society.

WHO position on influenza vaccines

The main purpose of influenza vaccination is to avoid severe influenza and its complications. This paper is concerned mainly with epidemic influenza and the public health impact of yearly influenza vaccination. Authoritative information on pandemics can be found in the WHO influenza pandemic plan (http://www.who.int/emc/diseases/flu/index.html). Recommendations for the use of inactivated influenza vaccines and other preventive measures are published in the *Weekly Epidemiological Record.*

Most of the widely licensed influenza vaccines are manufactured according to the quality requirements defined by WHO and have proven efficacious in the elderly and other groups at risk. If influenza vaccination of children is required, for example as a consequence of predisposing conditions, the vaccine will not interfere with diphtheria-pertussis-tetanus (DTP) or other childhood vaccines, possibly due at the same time. To reduce adverse effects, only split-vaccines or subunit vaccines should be given to children. Influenza vaccine should not be given to children aged under six months, and those aged 6–35 months should only receive half the adult vaccine dose.

Ideally, when major outbreaks are expected, all individuals should have the opportunity to be vaccinated against influenza. However, limited health budgets and, at least initially, shortage of the appropriate vaccine may force health authorities to restrict influenza vaccine to groups at particular risk. The following priority is recommended:

- Residents of long-term care facilities for the elderly and the disabled are considered at high risk of influenza and its complications.
- Elderly non-institutionalized individuals suffering from chronic conditions such as pulmonary or cardiovascular illness, metabolic diseases including diabetes mellitus and renal dysfunction, and various types of immunosuppression including persons with AIDS and transplant recipients.

- All adults and children aged over six months suffering from any of the conditions mentioned above.
- Individuals who are above a nationally defined age limit irrespective of other risk factors. Although the appropriate age for general vaccination may be considerably lower in countries with poor living conditions, most countries define the limit age as over 65 years.
- Other groups defined on the basis of national data.
- Health care workers in regular, frequent contact with high-risk persons.
- Household contacts of high-risk persons.

Pregnant women who will be in their second or third trimester by the start of the influenza season and who are likely to be exposed are advised to consider vaccination in careful consultation with a competent health care provider. From a societal perspective, there are good arguments for influenza vaccination of children and healthy adults. Where adequate vaccine supplies are available, vaccination of the general public may be considered. However, the implementation of large-scale influenza vaccination programmes for these groups requires further evaluation of cost-effectiveness and can not be generally recommended until firm data are presented. Nevertheless, persons who provide essential community services should be considered for vaccination. In some developed countries, companies find it economically justifiable to offer vaccination to their employees.

In many developing countries, the potential impact of influenza on morbidity and mortality as well as its economic burden is largely unknown and partially neglected. Considering the impact that poor living conditions have on the general health status, it is likely that influenza may significantly influence the levels of morbidity and mortality in such regions. In order to estimate the disease impact in these areas, WHO strongly encourages the implementation of epidemiological studies of influenza and that these data be used to conduct relevant intervention studies.

Although the WHO global influenza surveillance network has proven to be a reliable and successful system, it is important to increase worldwide coverage. Many countries are not included in the network, and in some large countries more than one centre is required. Surveillance is of particular importance in rural areas where potential animal hosts and humans live in close proximity, since it is in such areas that new viral recombinants are likely to originate.

The relatively low uptake of influenza vaccines in most industrialized countries implies that significant proportions of the groups at risk of complications from influenza are not vaccinated. WHO strongly emphasizes the importance of raising the public consciousness of influenza and its complications as well as of the beneficial effects of influenza vaccination.

WHO has issued guidelines on preparedness for a pandemic (available on the Internet at www.who.int/emc/diseases/flu/index.html).

This chapter was last published as a WHO position paper: Influenza vaccines. WHO position paper. *Weekly Epidemiological Record,* 2002, 77:230–238, and is available on the Internet at http://www.who.int/wer/pdf/2002/wer7728.pdf.

Administration summary

Type of vaccine	Inactivated, non-infectious viral
Number of doses	One, given by the subcutaneous or intramuscular route
Schedule	Before the influenza season starts
Booster	Boosters are unhelpful as the composition of the wild virus changes each year; one dose of the appropriate vaccine strains is needed annually
Contraindications	Severe hypersensitivity to egg or to previous dose
Adverse reactions	Local pain or tenderness, fever, malaise
Special precautions	None

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Japanese encephalitis vaccine

Summary and conclusions

Japanese encephalitis (JE) is the most important form of viral encephalitis in Asia, causing at least 50 000 cases of clinical disease and 10 000 deaths each year, mostly among children. In recent decades outbreaks of JE have occurred in several areas previously non-endemic for the disease, and the high fatality rate and frequent residual neuropsychiatric sequelae in survivors make JE a considerable public health problem in many Asian regions. Mosquitoes transmit the JE virus from viraemic animals, mostly domestic pigs, to humans at seasonal intervals. There is no drug treatment for JE, and although improvements in agricultural practices have contributed to the reduction in disease incidence in some countries, JE vaccination is the single most important control measure. Currently, three types of JE vaccines are in large-scale use:

- a mouse-brain-derived and inactivated vaccine based on the Nakayama strain (or on Beijing-1 strain) is produced in several Asian countries, and is currently the only vaccine available on the international market;
- a cell-culture-derived inactivated vaccine; and
- a cell-culture-derived live attenuated vaccine produced in China and widely used within the Chinese JE control programme.

Controlled studies performed in two different disease-endemic regions have shown that the mouse-brain-derived vaccine is efficacious and without serious side-effects for childhood vaccination. In view of recent reports of allergic reactions occurring in about 0.6% of adult Western recipients of this vaccine, increased alertness with regard to adverse side-effects among vaccinees in JE-endemic areas is warranted. So far, there is no indication of reduced protective efficacy of the current mouse-brain-derived vaccine in areas where the prevailing JE virus strains show antigenic or genetic differences from Nakayama or Beijing vaccine strains.

- JE immunization of children using the mouse-brain-derived inactivated vaccine should continue according to established schedules in regions where this vaccine has already been successfully introduced, preferably as part of the national immunization services.
- Efforts should be made to explore optimal immunization schedules and possible synchronization with national immunization services, and to evaluate the need for booster injections.
- Where affordable, JE vaccination should be extended to all disease-endemic areas where JE is considered a public health problem.

- The apparent occurrence of allergic adverse effects observed among adult recipients of this vaccine in Western countries should result in intensified surveillance for adverse effects among vaccinated children and adults in disease-endemic areas.

The development of efficient, safe and appropriately priced alternatives to the commercially available vaccine should be given high priority.

Public health impact

JE is an acute viral infection of the central nervous system occurring in a large number of countries/areas of Asia, including Cambodia, China, Indonesia, Japan, Lao People's Democratic Republic, Malaysia, Myanmar, the Philippines, Republic of Korea, Thailand, Viet Nam, south-eastern Russian Federation and the Indian subcontinent. In recent decades, JE has gradually spread to previously non-affected Asian regions, and a small outbreak was recently reported from islands in the Torres Strait off the Australian mainland.

The annual incidence of clinical infection in disease-endemic areas ranges from 10-100 per 100 000 population. Close to 3 thousand million people are now living in JE-endemic regions, where more than 70 million children are born each year.

Bloodsucking *Culicine* mosquitoes (mainly *Culex tritaeniorhynchus, Cx. gelidus* and *Cx. fuscocephala*) transfer the virus to humans from infected animals, in most cases domestic pigs and wading birds. Human beings are not considered a reservoir for viral transmission. The virus infection rate in the mosquito vector ranges from less than 1% to 3%. *Culex* breeds preferably in water pools and flooded rice fields, and most of the human cases occur in rural areas. However, outbreaks have occurred also in periurban and urban populations of several major Asian cities. In most regions the period of transmission starts in April or May, and lasts until September or October. In some tropical and subtropical areas the incidence peaks during and shortly after the rainy season, the timing depending on the region. However, where irrigation permits mosquito breeding throughout the year, transmission may occur even in the dry season.

Serological surveys show that most of the people living in JE-endemic areas are infected with the virus before the age of 15. Usually, however, the infection does not cause clinical symptoms; an estimated average of 1 in 300 JE viral infections results in symptomatic illness. In hyperendemic areas, half the number of cases occur before the age of four years, and almost all before the age of 10 years. In countries such as Japan and the Republic of Korea, and in some regions of China, the incidence of JE has decreased over several decades, in part due to extensive use of JE vaccines, but also as a consequence of improving socioeconomic conditions and changing agricultural practices. In some of those regions a shift is also observed in the age distribution of cases towards older children and adults. In Japan, the age-specific incidence has become bimodal, peaking in young children and the elderly. The disease is uncommon among short-term visitors and tourists to JE-endemic areas.

The clinical disease follows an incubation period of 4–14 days and is mostly characterized by sudden onset of fever, chills and aches, including headaches and sometimes meningismus, particularly in adults. In children, gastrointestinal pain and dysfunction may dominate the initial stage of the disease. Convulsions are also very common in paediatric patients. Although JE is often a mild disease, leading to an uneventful recovery, some cases rapidly progress to severe encephalitis with mental disturbances, general or focal motor abnormalities, and progressive coma. Of the approximately 50 000 cases of JE officially reported each year, about 10 000 end fatally, and a very high percentage of the survivors are left with neurological and psychiatric sequelae, requiring extensive care. Most fatalities and residual sequelae occur in children aged over 10 years.

Since most infections occur in childhood, experience with JE disease in pregnant women is limited. However, studies from Uttar Pradesh (India) indicate a high risk of abortion among those infected during the first two trimesters. The potential impact of concurrent infections (in particular HIV) on the outcome of JE virus infection is not yet established. Also, several aspects of JE epidemiology require further study. Examples of problems in need of further investigation include the reasons for the geographical distribution and the mechanisms of viral persistence between epidemics.

The pathogen

Japanese encephalitis virus (JEV) belongs to the flavivirus family. Flaviviruses have single-stranded RNA, are spherical, enveloped and about 40 nm in diameter, and are usually vectorborne. JEV is antigenically related to several other flaviviruses, including St. Louis encephalitis virus and West Nile virus. Virus-specific as well as cross-reactive neutralizing epitopes for JE have been identified on the envelope glycoprotein. A number of antigenic subgroups of the virus are known, although so far, possible differences between these subgroups in terms of virulence or host preferences are poorly defined. Following an infectious mosquito bite, the initial viral replication occurs in local and regional lymph nodes. Viral invasion of the central nervous system probably occurs via the blood. Certain neurotransmitter receptors are believed to be involved in the binding of JE virions to cells in the central nervous system. The affinity of JE virus for neural tissue leads to propagation in the brain.

The aetiological diagnosis of JE is mainly based on serological testing, using IgM-capture ELISA, that detects specific IgM in the cerebrospinal fluid or in the blood of almost all patients within four to seven days of disease onset. Other diagnostic methods include recently developed dot-blot or immuno-precipitation IgM assays, suitable for use in the field, and traditional tests that monitor significant changes of JE-specific antibody titres in sequential serum samples. The virus may be recovered in various cell cultures inoculated with blood collected during the early stages of the disease, or from the cerebrospinal fluid (or brain) in advanced cases of encephalitis. Polymerase chain reaction-based tests for the detection of virus-specific genomic material, particularly in cerebrospinal fluid, have also been developed.

Protective immune response

Protection is associated with the development of neutralizing antibodies. Although no international standard has yet been established, neutralizing antibody titres of 1:10 or more are commonly accepted as evidence of protection. A role for cell-mediated immune mechanisms in protection against JE virus has been demonstrated in experimental studies on mice.

The justification for vaccination

JE is the leading cause of viral encephalitis in Asia. In disease-endemic areas, annual incidence of clinical disease ranges from 10–100 per 100 000 population. Case fatality averages 30% and a very high percentage of the survivors are left with permanent neuropsychiatric sequelae. There is no efficient drug treatment for this disease. In recent decades the JE virus has caused epidemics in previously unaffected countries, including India, Myanmar, Nepal, Sri Lanka, Thailand and Viet Nam. No effective method of environmental control of JE transmission is known. Although socioeconomic improvements and changes in agricultural practices are likely to reduce viral transmission in some places, large-scale vaccination of affected populations with effective and affordable vaccines appears to be the logical control measure, at least in the short term. The impact of large-scale JE vaccination is clearly documented in some regions of China, and systematic vaccination has also probably contributed significantly to the declining incidence rates in Japan, Republic of Korea and Thailand.

Vaccines against Japanese encephalitis

Three types of JE vaccine are currently in large-scale production and use, namely:

- Mouse-brain-derived inactivated vaccine;
- cell-culture-derived inactivated vaccine; and
- cell-culture-derived live attenuated vaccine.

(i) Mouse-brain-derived inactivated vaccine

The mouse-brain-derived inactivated JE vaccine is produced in several Asian countries. So far, this is the only type of JE vaccine that is commercially available on the international market. Crude versions of such vaccines were produced as early as the 1930s. However, variable immunogenicity and fear of vaccine-induced encephalitis owing to their high content of myelin basic protein prompted the development of the current vaccine, which is produced to secure consistent immunogenicity, and which has an extremely low content of myelin basic protein (< 2 ng per ml). The commercially available mouse-brain-derived JE vaccine is based either on the Nakayama strain, which was isolated in Japan in 1935, or on the Beijing-1 strain. This vaccine has proved to be efficacious even in Thailand, where different topotypes of the JE virus are prevalent. On the other hand, cross-immunization studies in mice comparing the Nakayama strain with JE virus strains from different Asian regions have shown that the so-called Beijing-1 strain induces a broader neutralizing antibody response. For this reason, and because of the higher antigen yield in the mouse brain following inoculation of the Beijing strain, the Nakayama strain has been replaced in several mouse-brain-derived JE vaccines.

The mouse-brain-derived JE vaccine is given subcutaneously in doses of 0.5 ml or 1 ml, the lower dose being for children aged one to three years. Due to likely interference with remaining maternal antibodies, children are usually not vaccinated before the age of one year. The manufacturers of the internationally marketed vaccine recommend that primary childhood immunization involve two injections at an interval of one to two weeks. In several Asian trials, primary immunization has a disease-preventing efficacy of more than 95%; 91% efficacy was achieved in a placebo-controlled trial. The seroconversion rates appear not to be reduced when other childhood vaccines are given simultaneously. However, the primary vaccination schedules vary considerably among different Asian countries. Furthermore, the optimal intervals and number of booster doses are poorly defined, and may show considerable local variation reflecting, for example, a different boostering impact of prevailing cross-reacting flaviviruses. Many Asian countries have adopted a schedule of two primary doses approximately four weeks apart, followed by a booster after one year, with subsequent boosters at three-year intervals. However, the duration of immunity after serial booster doses has not been well established.

Immunogenicity studies conducted in Western countries, where interference by other flaviviruses is unlikely, has shown that seroconversion was obtained only in about 80% of the vaccinees following the primary two-dose schedule. Also, in 90% of the vaccinees the titre of neutralizing antibody declined within 6–12 months to levels below the established protective titre level. However, in United States soldiers, a three-dose schedule based on vaccination on days 0, 7 and 30 resulted in 100% seroconversion, significantly higher titres of neutralizing antibodies, and persistence of those high levels for at least three years.

In its lyophilized version, this vaccine is stable at 4°C for at least one year; following reconstitution it retains its original potency for at least two weeks at 22°C, whilst at 37°C, potency is still 85% after two weeks. This stability obviously facilitates its use under field conditions in hot climates. In disease-endemic regions of Thailand, JE vaccination has been successfully incorporated into the national immunization service. However, owing to its relatively high price, large-scale vaccination with the mouse-brain-derived JE vaccine is unlikely to be affordable in the poorest countries of Asia.

In general the mouse-brain-derived JE vaccine has been considered relatively safe, although local reactions such as tenderness, redness and swelling occur in about 20% of the vaccinees. A similar percentage may experience mild systemic symptoms, including headache, myalgia, gastrointestinal symptoms and fever. Vaccine-related neurological complications were not observed in Japanese studies from 1955–1966. However, in recent years, several cases of acute encephalitis temporally linked to JE vaccination have been reported. From the Republic of Korea, three such cases were recently reported, of which two were fatal. Furthermore, hypersensitivity reactions, in some cases serious generalized urticaria, facial angiooedema or respiratory distress, have recently been observed in adult Western vaccine recipients. In 1994, two cases of fatal anaphylaxis attributed to JE vaccinations were observed in the Republic of Korea. In a prospective study among United States military personnel in Okinawa (Japan), the overall allergic reaction rate was 62.4 per 10 000 vaccinees. Most reactions were mild to moderate, but 2.6 per 10 000 vaccinees were hospitalized. Persons with a history of previous allergic reactions were more prone to develop hypersensitivity to the vaccine. The vaccine components responsible for these adverse

effects have not been identified, although allergic reactions to gelatin which is used to stabilize the vaccine is suspected in some of the cases. Such reactions may occur as late as 12–72 hours following immunization. Except for a history of hypersensitivity to the vaccine, there are no contraindications to JE vaccination.

(ii) Cell-culture-derived inactivated vaccine

This vaccine is manufactured in China and based upon the Beijing P-3 strain of JE virus, which provides broad heterologous immunity in mice, and high viral yields when propagated in primary hamster kidney cells. Primary immunization of infants with this formalin-inactivated vaccine results in about 85% protection. The vaccine is inexpensive, and 90 million doses are distributed for use in China every year, although it will gradually be replaced by the cell-culture-derived live attenuated vaccine.

(iii) Cell-culture-derived live attenuated vaccine

This Chinese vaccine is based on a stable neuro-attenuated strain of the JE virus (SA-14-14-2). When administered in areas that were not JE-endemic, one single dose of this vaccine induced an antibody response in 83%–100% of children aged six to seven years, and in older children immunized twice at intervals of one to three months, 94%–100% showed a serological response. Side-effects are reported to be minimal. The cost per dose in China is very low. Currently, 40 million doses of this vaccine are produced annually for use in China.

WHO position on Japanese encephalitis vaccines

Only a freeze-dried, mouse-brain-derived vaccine based on either the Nakayama or Beijing strain of the JE virus is commercially available internationally. This vaccine is manufactured according to current international quality requirements, and is in general considered efficient and safe for immunization of children. At least in Thailand, the JE vaccine has been successfully incorporated in the national immunization service, and there is no evidence of interference with simultaneously given vaccines. Hence, where affordable, this vaccine is recommended for use in JE-endemic regions.

Rare, but serious, neurological side-effects attributed to this JE vaccine have been reported from disease-endemic as well as non-endemic regions. Also, about 0.6% of Western adults, who in recent years were vaccinated prior to visits to JE-endemic areas, have experienced allergic reactions to components of this vaccine. Therefore, an increased awareness of neurological as well as allergic adverse effects is necessary in endemic areas, in particular in countries where changing epidemiological patterns motivate JE vaccination of adults as well as children. Phase IV studies, including the required system for surveillance and reporting of rare events, should be performed in children. The possibly higher incidence of adverse reactions in adults may be addressed in appropriately powered placebo-controlled trials.

Although several of the JE-endemic Asian countries produce the mouse-brain-derived vaccine for their national consumption, there is a problem of vaccine supply in many disease-endemic areas. Unfortunately, the price of the commercially available vaccine is an obstacle to its use in many of the poorest countries in the region.

Although both genotypic and phenotypic variations of JE viruses have been demonstrated, there is little evidence to suggest that the Nakayama vaccine strain results in reduced protection against infection by local virus strains.

Further information is needed concerning the duration of protection induced by JE vaccination. The practice of repeated immunization with JE vaccine requires careful review. It is not known whether exposure of vaccinated individuals to natural infection contributes to protection. The possible interaction between JE virus infection and other flaviviruses prevailing in the regions concerned requires further study. At least in theory, interactions between related flaviviruses could have an impact both on the result of primary immunization and on the requirement for boosters.

Effective and inexpensive JE vaccines are needed in large quantities in order to meet WHO and national public health objectives.

This chapter was last published as a WHO position paper: Japanese encephalitis vaccines. WHO position paper. *Weekly Epidemiological Record*, 1998, 73:337–344, and is available on the Internet at http://www.who.int/wer/pdf/1998/wer7344.pdf.

Administration summary

Type of vaccine	Inactivated mouse-brain-derived
Number of doses	Standard three-dose schedule, or reduced two-dose schedule subcutaneous
Schedule	Three doses at days 0, 7 and 28; or two doses given one to four weeks apart (0.5 ml for children)
Booster	Most countries give a booster after one year, then three-yearly
Contraindications	Hypersensitivity to previous dose
Adverse reactions	Occasional mild local or systemic reactions; occasional severe reaction with generalized urticaria, hypotension, collapse
Special precautions	Avoidance of mosquito bites; this is as important as immunization

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Measles vaccine

Public health strategies

Measles is a highly contagious viral infection that affected almost every person by adolescence during the pre-vaccine era. Transmission primarily occurs in large respiratory droplets. The disease typically consists of high fever, cough, runny nose and generalized maculopapular rash. Complications such as diarrhoea, middle-ear infection and pneumonia are common. Infants under one year of age have the highest case-fatality rates, sometimes reaching 20% in epidemics.

The use of measles vaccine in infant immunization services globally has led to a significant reduction in measles cases and deaths. In addition to providing direct protection to the vaccinee, immunization results in the indirect protection of unimmunized persons, i.e. in herd immunity, if high enough coverage is achieved. Measles vaccine has several major effects on the epidemiology of the disease. These include an increase of the mean age of infection and in the time between epidemics.

WHO perspective

Despite the availability of an effective measles vaccine for almost 40 years the disease still causes a considerable burden in many countries, primarily because of underutilization of the vaccine. In 2001 it was estimated that there were 30 million measles cases and 777 000 deaths. Most deaths occurred in developing countries, principally in Africa and Asia. Thirteen countries reported that routine measles vaccine coverage was below 50%. Large measles outbreaks continue to occur, especially in areas of developing countries with low vaccine coverage and among children living in countries where there are complex emergencies. Moreover, these outbreaks frequently have high case-fatality rates. In order to combat this situation the WHO/UNICEF Global Measles Strategic Plan 2001–2005 seeks to reduce measles mortality worldwide in a sustainable way by 50% relative to 1999 estimates.

The strategies recommended for reducing measles deaths include the following.

- A dose of measles vaccine should be provided to a very high proportion of infants at nine months of age or shortly thereafter through routine immunization services. This is the foundation of the sustainable measles mortality reduction strategy.

- All children should have a second opportunity to receive measles vaccine. This increases the proportion of children who receive at least one dose and helps to assure measles immunity in previously vaccinated children who failed to develop such immunity.The second opportunity may be delivered either through routine immunization services or through periodic mass campaigns.
- Measles surveillance should be strengthened through the integration of epidemiological and laboratory information.
- The clinical management of measles cases should be improved.

Special issues

Vitamin A and malnutrition: In order to promote overall improvements in child health, measles vaccination should be used as an opportunity to administer supplementary doses of vitamin A in areas where a deficiency of this vitamin is prevalent. Opportunities to do so occur during:

- routine measles vaccination (e.g. at nine months of age);
- national immunization days;
- measles supplementary campaigns.

Many children experience uncomplicated measles and require only supportive measures, including vitamin A treatment, nutritional support and education for mothers about complications. However, a significant proportion of measles cases in developing countries can be expected to have at least one complication and some may involve multiple systems. It is vital that measles cases, whether isolated or in outbreaks, receive vitamin A supplementation as part of the measles treatment.

HIV-infected children: Children with known or suspected HIV infection are at increased risk of severe measles and should be offered measles vaccine as early as possible. Such infants should receive measles vaccine at six months of age, followed by an extra dose at nine months. The overall risk to them of the vaccine causing adverse events is low compared with the risk of measles infection and its complications. Where the chance of contracting wild-type measles virus infection is almost non-existent, countries with the capacity to monitor an individual's immune status may consider withholding measles vaccine from severely immunocompromised, HIV-infected children, but children with moderate levels of immune suppression should continue to receive measles vaccine.

Combination with rubella vaccine: Countries should assess their rubella situation and, if appropriate, make plans for the introduction of rubella vaccination through the use of combined MR or MMR vaccines. The choice of policy depends on baseline information concerning the susceptibility profile of women of childbearing age. Surveillance for congenital rubella syndrome, as outlined in the WHO guidelines, should be initiated.

Pregnancy: Although there is no evidence that measles vaccine administered during pregnancy has adverse effects on the developing fetus, it is prudent, as with other live vaccines, to avoid the administration of measles vaccine to pregnant women.

Measles outbreak control: Because of the very high communicability of measles, many susceptible persons may have been infected before an outbreak is recognized and control activities are implemented. It is therefore very difficult to control measles outbreaks effectively through supplementary immunization activities. The priority during a measles outbreak is to reduce the number of deaths by ensuring good case management and vitamin A supplementation. If the attack rate is comparatively high in children aged under nine months, careful consideration should be given to temporarily lowering the age of routine vaccination to six months for the duration of the outbreak. Children immunized at six months of age should receive an additional dose of measles vaccine at nine months. If immunization activities are conducted in outbreak situations they should target neighbouring areas that are still unaffected, i.e. areas to which the outbreak is likely to spread.

If measles outbreaks occur in refugee camps, among internally displaced people, hospitals and military barracks, the immediate implementation of supplementary immunization activities is required. In refugee camps, the vaccination of all children aged less than 12 years is indicated as soon as they arrive. Delay may result in high morbidity and mortality.

Public concern: Since 1998 it has been postulated that the receipt of MMR vaccine may be associated with autism, Crohn's disease and other bowel abnormalities. However, no causal relationship has been proved between immunization with measles-containing vaccines and these events. A careful review of data has not found any evidence to confirm a causal association. WHO continues to recommend the use of MMR vaccines on the basis of their proven record of effectiveness and safety.

Administration summary

Type of vaccine	Live attenuated viral
Number of doses	One dose given by the intramuscular or subcutaneous route, with opportunity for second dose at least one month after the first
Schedule	At 9–11 months of age in countries where measles is highly endemic*, later in countries with high levels of control or low mortality
Booster	A second opportunity for immunization is recommended (routine or campaign)
Contraindications	Severe reaction to previous dose; pregnancy; congenital or acquired immune disorders (not HIV infection)
Adverse reactions	Malaise, fever, rash 5–12 days later; idiopathic thrombocytopenic purpura; rarely, encephalitis, anaphylaxis
Special precautions	None

* Infants at high risk (HIV-infected, in closed communities such as refugee camps, or in the presence of an outbreak) should have an additional dose at six to nine months.

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Meningococcal vaccines

(Polysaccharide and polysaccharide conjugate vaccines)

Summary and conclusions

Meningococcal meningitis and septicaemia are caused by various serogroups of *Neisseria meningitidis*. Endemic disease occurs worldwide and is mostly caused by meningococci of serogroups A, B, or C, although group Y is gaining importance, at least in parts of the United States. The group A meningococcus is the predominant cause of large epidemics. Particularly in the so-called "African meningitis belt" major group A epidemics occurring at intervals of 7–14 years result in excessive morbidity and mortality among children and young adults. In recent years also group W135 meningococci have caused an outbreak in this region as well as in Saudi Arabia, whereas several Western countries have experienced outbreaks of group C strains.

Meningococcal disease is associated with high case-fatality rates (5%–15%) even where adequate medical services are available. Chemoprophylactic measures are in general insufficient for the control of this disease.

Immunity following meningococcal infection is serogroup specific. Current internationally marketed meningococcal vaccines are based either on combinations of group-specific capsular polysaccharides (A and C or A,C,Y, and W135) or on a conjugate between group C specific polysaccharide and a protein carrier. The polysaccharide vaccines are safe and highly immunogenic, although the group C component is ineffective in children under two years of age. On the other hand, the recently introduced serogroup C conjugate vaccine is safe and efficacious even in the youngest children. Monovalent polysaccharide vaccines are not readily available and, so far, no group A conjugate vaccine has reached the market. Vaccines against group B meningococci have shown only modest efficacy both in children and adults.

The emphasis of this chapter is on internationally available meningococcal polysaccharide vaccines and polysaccharide conjugate vaccines. Current internationally available meningococcal polysaccharide vaccines are safe and effective for individuals aged two years or more and are recommended for routine immunization of specific risk groups above this age.

Group A polysaccharide shows poorer immunogenicity and shorter duration of protection in those below two years of age, and group C polysaccharide is not immunogenic in that age group. Groups A and C polysaccharide vaccines are therefore not generally used in routine infant immunization services.

Meningococcal polysaccharide vaccines are also recommended for use in controlling epidemics of meningococcal disease caused by serogroups included in the vaccine through large-scale emergency immunization of the population at risk. (As part of emergency immunization combined groups A and C vaccines may also be given to children below two years of age).

Non-conjugated group C polysaccharide vaccines may, if given to young infants, lead to reduced responsiveness to this antigen in later years. The clinical significance of this is unclear. The recently introduced meningococcal group C conjugate vaccines have proved to be safe and efficacious in all age groups including infants, and are easily adapted to the timing of routine childhood immunization services.

Group C conjugate vaccines are recommended for inclusion in national childhood immunization services, for protection of high-risk individuals, as well as for targeted vaccination during outbreaks, depending on the epidemiological situation, public health priorities and economy of the concerned countries.

Meningococcal polysaccharide antigens of groups A, C, Y and W135 do not provide any protection against group B meningococci, which in some countries are the leading cause of endemic meningococcal disease. In future, widespread use of improved groups A, B, C, Y and W135 vaccine combinations in routine childhood programmes may ultimately eliminate the need for emergency mass immunization against meningococcal disease. There is a considerable need for improved bacteriological surveillance, including incidence by serogroup, of meningococcal disease, particularly in low-income countries.

Public health aspects

Neisseria meningitidis (the meningococcus) is a leading cause of meningitis and fulminant septicaemia and a significant public health problem in most countries. Although meningococcal disease frequently occurs as scattered, apparently unrelated cases or in small outbreaks, in some regions this situation may alternate with devastating, unpredictable epidemics. Thus, during explosive epidemics in sub-Saharan Africa, incidence rates of up to 1000 cases per 100 000 inhabitants have been reported. In 1996, an epidemic involving several West African countries caused approximately 250 000 cases and 25 000 deaths. Another major epidemic in that region occurred in 2000–2001. Globally, about 500 000 cases and 50 000 deaths are caused by this pathogen each year.

As a rule, endemic disease occurs primarily in children and adolescents, with highest attack rates in infants aged 3–12 months, whereas in meningococcal epidemics, rates may rise in older children and young adults. In sub-Saharan Africa, endemic and epidemic disease strikes primarily children and adolescents.

Most untreated cases of meningococcal meningitis and/or septicaemia are fatal. In industrialized countries, the overall mortality from meningococcal meningitis is usually 5%–10%; in Africa, it is closer to 10%. Case-fatality rates in fulminant septicaemia may exceed 15%–20%. About 10%–15% of those surviving meningococcal meningitis will suffer from significant neurological sequelae, including mental disorders, deafness, palsies and seizures. Extensive tissue necrosis, sometimes resulting in amputations, may also occur.

Meningococcal serogroups A, B and C are responsible for the vast majority of morbidity and mortality. Serogroup A is the cause of most major epidemics: Explosive group A outbreaks in cycles of 7–14 years typically occur in countries of the so-called meningitis belt which extends across Africa from Senegal to Ethiopia. Such group A epidemics are usually due to a single strain of the pathogen. Since 1988, related strains of the III-1 clone have caused major outbreaks in Africa and parts of Asia. In other areas of the world, group A infections are less common, and groups B and C cause most meningococcal disease. In the 1980s and 1990s group C meningococci of the ET-37 complex (including ET-15) caused clusters of meningococcal disease in Australasia, Canada, and the United States, as well as in several European countries, often attacking adolescents and young adults. Group B epidemics have occurred in Europe, Latin America and New Zealand in the past 20 years, although an endemic disease pattern predominates. In most parts of the world, serogroups Y and W135 are relatively uncommon causes of meningococcal infection. However, recent reports of endemic occurrence of group Y meningococcal disease in the United States, and outbreaks caused by group W135 strains in Saudi-Arabia and sub-Saharan Africa, particularly Burkina Faso, suggest that these serogroups may be gaining importance, at least among young adults.

Nasopharyngeal carriage of meningococci is most common (5%–15%) among adolescents and young adults, less so among young children and relatively rare (1%) in adult populations. Transient nasopharyngeal carriage rather than disease is the normal outcome of meningococcal colonization. Information is incomplete with regard to conditions influencing the balance between asymptomatic carriage and bacterial invasion, but they are likely to include factors such as virulence of the bacterial strain, state of non-specific as well as specific immunity, interference of viral infections, nutritional status, environmental factors such as air pollution (dust, smoking) and climatic conditions.

In the meningitis belt, the epidemics typically start during the dry season (January–March) and end at the onset of the rainy season (May–June). Between the great epidemics, these regions are often hyperendemic for meningococcal disease, with small outbreaks and numerous sporadic cases. In temperate climates, endemic meningococcal disease peaks during the winter and spring.

The pathogen

Meningococci are aerobic, Gram-negative, encapsulated bacteria commonly occurring in pairs (diplococci). These bacteria are readily isolated from nasopharyngeal secretions and cultured on laboratory media. At least 12 serogroups, characterized by differences in the polysaccharide capsule, have been identified; groups A, B and C account for about 90% of meningococcal disease. Differences in the outer membrane proteins are used to further distinguish different serotypes and subtypes. Genomic typing such as multilocus enzyme electrophoresis typing (ET) and multilocus sequence typing allow determination of clonal relatedness and have greatly enhanced the understanding of the dynamics of meningococcal carriage and spread. The polysaccharide capsule and the lipopolysaccharide component (endotoxin) of the bacterial cell wall are important virulence factors. Group III strains of serogroup A, the ET-5 complex strains of serogroup B and strains of the ET-37 complex of serogroup C are all important causes of recent meningococcal outbreaks.

N. meningitidis is transmitted by aerosol or direct contact with respiratory secretions of patients or healthy human carriers; there is no animal or environmental reservoir for this organism.

In most parts of the world meningococci are still highly susceptible to penicillin, which is usually the drug of choice for treatment, although a single dose of oily chloramphenicol may be the preferred treatment in areas with limited health facilities. Other drugs, such as rifampicin, are required to eradicate nasopharyngeal colonization. In recent years the occurrence of meningococcal isolates with reduced sensitivity to penicillin have been reported mainly from Spain.

Immune response

Humoral immunity is essential in the resistance to meningococcal disease, whereas the corresponding role of T-cell dependent immunity is poorly defined. Susceptibility to systemic disease is linked to an absence of detectable bactericidal antibodies. Passively transferred maternal antibodies protect infants against meningococcal infections during the first few months of life, whereas high incidence rates are recorded in the age group 6–12 months. A progressive increase in the proportion of children with bactericidal antibodies in the age group 2–12 years coincides with a decrease in the incidence of meningococcal disease. The persistence of this protection may depend in part upon bactericidal antibodies induced by cross-reacting microbial antigens and occasional nasopharyngeal colonization by meningococcal strains. Protection is usually group-specific, and for serogroups A, C, Y and W-135 protection appears largely to be due to anti-polysaccharide antibodies. Some investigators suggest that bactericidal anti-C and anti-A antibody levels in excess of 1µg/ml are protective.

Justification for vaccine control

N. meningitidis is one of the most common causes of bacterial meningitis in the world and the only bacterium capable of generating large epidemics of meningitis. Rapid progression of meningococcal disease frequently results in death within one or two days of onset, or in severe sequelae, even in cases of apparently optimal medical treatment. Chemoprophylaxis may prevent secondary cases among close contacts, but since secondary cases comprise only 1%–2% of all meningococcal disease, chemoprophylaxis is of little value for the control of most endemic and epidemic disease. As 5%–15% of children and young adults carry meningococci in the nasopharynx, control of meningococcal disease based on chemo-therapeutic elimination of nasopharyngeal carriage is practically impossible except in small and relatively closed communities. Hence, immunization using safe and effective vaccines is the only rational approach to the control of meningococcal disease. In situations where vaccines are not available, enhanced case management is the recommended strategy.

Meningococcal vaccines

Polysaccharide vaccines: Internationally marketed meningococcal polysaccharide vaccines are either bivalent (groups A and C) or tetravalent (groups A, C, Y and W135). The vaccines are purified, heat-stable, lyophilized capsular polysaccharides from meningococci of the respective serogroups. The recommended single dose of the reconstituted vaccine contains 50 mg of each of the individual polysaccharides. These vaccines are very safe, and significant systemic reactions have been extremely rare. The most common adverse reactions are erythema and slight pain for one or two days at the site of injection. Fever exceeding 38.5°C occurs in 1%–4% of the vaccinees. No significant change in safety or reactogenicity has been observed between bivalent or tetravalent meningococcal vaccines.

Both group A and group C polysaccharides have documented short-term efficacy levels of 85%–100% in children aged two years or more and in adults. In infants of three months neither of the polysaccharide vaccines reliably elicits protective antibodies. However, unlike other purified polysaccharide vaccines, repeated immunization in infancy and early childhood with group A meningococcal polysaccharides induces antibodies correlating with protection against group A meningococcal disease. By contrast, group C polysaccharide vaccines are not reliably immunogenic in children below two years of age, and if given to young infants, such vaccines may lead to tolerance to group C antigen in later years. Group Y and W135 polysaccharides have been proved to be safe and immunogenic only in children aged two years and above. When the groups A and C, or A, C, Y and W135 polysaccharides are administered together as bivalent or tetravalent vaccines, independent, group-specific immune responses are obtained. A protective antibody response occurs within 10–14 days of vaccination. In schoolchildren and adults, a single dose of groups A and C polysaccharide vaccine provides protection for at least three years. In contrast, in children less than four years of age, clinical protection and the levels of specific antibodies decline rapidly over the first two to three years following a single dose of the vaccine.

Group B polysaccharide is poorly immunogenic, even when conjugated to a protein carrier. This has been attributed to the similarity of the group B polysaccharide to antigens of the central nervous system.

Group C conjugate vaccines: A thymus-dependent immune response is achieved through conjugation of group C-specific meningococcal polysaccharide to a protein carrier. Three group C meningococcal conjugate (MCC) vaccines are currently licensed internationally. In two of these vaccines the polysaccharide is linked to a non-toxic mutant of diphtheria toxin (CRM 197) whereas in one vaccine tetanus toxoid is used as carrier protein. Both types of conjugate vaccines induce enhanced levels of IgG anti-capsular antibodies and memory B-cells. In late 1999 immunization against group C meningococcal disease using MCC vaccines became part of the national immunization service in the United Kingdom, where at that time the incidence of meningococcal serogroup C disease was approximately 2 per 100 000 population. Infants were vaccinated at two, three and four months of age and children aged 4–13 months and teenagers were offered catch-up vaccination.

Large-scale serological studies in the United Kingdom showed that, 16 months following vaccination with one single dose of the MCC vaccine, 88% of children aged one to two years still had protective antibody levels whereas among adolescents of 15–17 years 96% had protective levels. Preliminary data based on a serum bactericidal assay suggest that, in infants, three doses of MCC vaccine at intervals of two months provide high levels of protection. Following the introduction of MCC vaccination into the routine infant schedule and extensive catch-up vaccination of young children and teenagers there was a rapid decline in group C meningococcal disease. Moreover, careful surveillance has shown no evidence of changes of the prevalent serogroups and serotypes among invasive meningococcal isolates since the MCC programme was launched in the United Kingdom.

The United Kingdom experience confirms that the safety profile of the current MCC vaccines is excellent. Fortunately, previous immunization with unconjugated group C polysaccharide does not compromise the immune response to MCC vaccines and none of the MCC vaccines interferes with the response to co-administered vaccines of the national UK immunization service. Although clearly inducing immunological memory the period of observation is too short to allow conclusions on the duration of protection in the various age groups. However, based on experience gained with the successful conjugate vaccine against *Haemophilus influenzae* type b, the MCC vaccines may be expected to provide high levels of protection for at least 10 years following completion of the three-dose course in infants or a single dose in adolescents. Furthermore, the observed relatively high post-immunization concentrations of mucosal anti group-C antibodies are likely to counteract colonization of group C meningococci and hence result in a herd immunity effect.

WHO position on meningococcal vaccines

WHO recommendations for the production and quality control of meningococcal polysaccharide vaccines are published in the WHO Technical Report Series (No 658, 1981) and corresponding recommendations for the conjugate vaccines will appear shortly in this series.

The internationally licensed polysaccharide vaccines against meningococcal disease, whether bivalent (groups A and C) or tetravalent (groups A, C, Y and W135) are all of documented safety and satisfactory immunogenicity in adults and children of more than two years of age. Also, these vaccines are relatively inexpensive compared with the conjugated group C vaccines that now are becoming available. Although group A polysaccharide may induce antibodies and immunological memory even in the youngest children, infants need two doses of group A-containing vaccine to induce adequate titres of antibody; without further boosting these titres decline to control levels within 18 months. At least four such doses during the first five years of life would be required to ensure protective antibody levels, and the safety and effectiveness of such a regimen have not been documented. Meningococcal group C polysaccharide is not immunogenic in children below two years of age. In addition, the immunological characteristics of the group Y and W135 polysaccharides appear to be similar to those of group C. Thus, several features of the currently available polysaccharide vaccines limit their utility in routine infant immunization services.

Emergency immunization using polysaccharide vaccines of groups A and C or A, C, Y and W135 are recommended to control outbreaks of meningococcal disease. Since meningococcal outbreaks tend to affect specific age groups, the precise target population for immunization may vary with the epidemiological situation. As emergency vaccination in most cases is in response to group A outbreaks, combined polysaccharide vaccines may also be offered to children below two years of age. However, during outbreaks of proven group-C aetiology, group C conjugate vaccines should be considered for protection of this age group, where possible.

Recent experience has shown that during major meningococcal outbreaks, the production capacity may be insufficient. This underlines the importance of having adequate emergency stores of appropriate meningococcal vaccines in regions where major epidemics tend to occur.

With polysaccharide vaccines there is no convincing demonstration of a herd immunity effect mediated through substantial reduction of meningococcal carriage. Therefore, during an outbreak, efforts should be made to reach all persons in high-risk groups who may benefit from the vaccine.

Implementation of mass immunization campaigns has contributed to control of major group A and group C epidemics throughout the world. However, in many areas additional work is needed to develop the surveillance and response capacity necessary to identify outbreaks and immunize affected populations rapidly enough to yield maximum benefit from the intervention.

In addition to their use in emergency mass campaigns, meningococcal vaccines are also recommended for groups in which a particularly high risk of disease has been documented. These include those attending army units, training camps, or boarding schools, travellers to epidemic areas, and persons with immunological predisposition to meningococcal disease (such as asplenia and inherited immunological deficiencies).

In children the duration of protection following one dose of group A and/or C meningococcal polysaccharide increases with age and recipients aged four years or more are likely to be protected for several years. Although routine immunization of school-age children has been adopted in several countries, careful assessments of the duration of protection in the respective settings are not available. The only study evaluating duration of protection in a high-risk area suggested a slow decline in efficacy over a three-year period in children who were initially immunized at four or more years of age.

Since 1999 a conjugate group C vaccine has been available internationally. It has proved to be safe and highly efficient in controlling group C meningococcal disease, for example in the United Kingdom. By contrast to group C polysaccharides, the group C conjugate vaccine elicits adequate antibody responses and immunological memory even in infants who are vaccinated at two, three and four months of age. There is no evidence of tolerance in the youngest age group and no interference with concurrent vaccines. Immune responses are achieved regardless of previous immunization with group C polysaccharide vaccines and sufficient titres of protective antibodies are maintained for at least several years. For these reasons, inclusion of

conjugated group C vaccine in the national immunization services should be considered in areas where group C meningococcal disease is a substantial public health problem among young children. In older children and adolescents group C disease may be prevented by a single dose of this vaccine. Where disease in children above two years of age is the main concern, or where resources are limited, several years of protection may be achieved by single injection of the combined groups A and C polysaccharide vaccine.

A private-public consortium involving a major vaccine manufacturer and key international organizations has been established to speed up the development of new group A conjugate vaccines. As compared to the current polysaccharide vaccines, future group A conjugate vaccines should be more efficacious, particularly in infants, reduce nasopharyngeal carriage, and induce protection of longer duration. Unfortunately, the price of conjugate vaccines is likely to limit their use in many of the countries that are most affected by meningococcal disease. There is also concern that the small number of manufacturers and products in the field of meningococcal vaccines will reduce competition and increase the price of the vaccines. For these reasons WHO encourages studies aiming at optimizing the currently available polysaccharide vaccines against meningococcal disease in different epidemiological settings.

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Administration summary

	Polysaccharide	Conjugate
Type of vaccine	Purified bacterial capsular polysaccharide (AC, AC/W135, Y)	Purified bacterial capsular polysaccharide conjugated to a protein (only serogroup C available)
Number of doses	One	Three doses for infants, one dose for older children
Schedule	–	–
Booster	Every three to five years	None
Contraindication	Severe adverse reaction to previous dose	Severe adverse reaction to previous dose
Adverse reactions	Occasional mild local reaction, mild fever	Occasional mild local reaction, mild fever
Special precautions	Children aged under two years of age are not protected by the vaccine	–

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Mumps vaccine

Summary and conclusions

Mumps, or *parotis epidemica* is a viral infection primarily affecting the salivary glands. Although mostly a mild childhood disease, mumps virus may also affect adults, among whom complications such as meningitis and orchitis are relatively common. Encephalitis and permanent neurological sequelae are rare complications of mumps. In most parts of the world the annual incidence of mumps is in the range of 100–1000 per 100 000 population, with epidemic peaks every two to five years. Peak incidence is found among children five to nine years of age. Natural infection with mumps virus is likely to confer lifelong protection.

All commercially available mumps vaccines are based on live, attenuated strains of the virus. Extensive use of these vaccines in industrialized countries has proved them to be safe and efficacious; so far about 500 million doses have been administered. Approximately 120 countries are using mumps vaccine in their national immunization services. Where sustained vaccination has been achieved the incidence of mumps has been significantly reduced. In general, adverse reactions to mumps vaccination are rare and mild.

Large-scale mumps vaccination is recommended in countries with an efficient childhood vaccination programme and sufficient resources to maintain high-level vaccination coverage. In such countries the combination of mumps vaccine with measles, or preferably, measles and rubella vaccines is recommended.

National decisions to implement large-scale mumps vaccination should be based on careful cost-benefit analyses. As insufficient childhood vaccination coverage may result in an unfortunate epidemiological shift in the incidence of mumps to older age groups, childhood mumps vaccination should aim at a 80% coverage rate, or higher. In countries with lower childhood coverage rates, mumps vaccination may also be offered to assumed non-immune children 9–12 years of age.

WHO recommends making mumps a notifiable disease. If a large proportion of the population remains seronegative for mumps, care should be taken to vaccinate adults considered to be at special risk. Regular serosurveillance will provide information on the susceptibility for mumps in various age groups.

Public health impact

Until recent decades mumps has been a common infectious disease in all parts of the world, with annual incidences ranging from approximately 0.1% – 1%, in certain populations even reaching 6%. In hot climates the disease is endemic throughout the year, whereas in temperate climates incidence peaks in late winter. Mumps is generally a mild, self-limiting disease, although complications such as meningitis, encephalitis or orchitis may occur. Asymptomatic pleocytosis (>5 leucocytes/mm^3) of the CSF is found in 50%–60% of mumps patients, whereas symptomatic meningitis is reported in up to 15% of the cases. Meningitis occurs more often in males than in females and adults are at a higher risk than children. Mumps encephalitis without signs of meningitis is reported in 0.02%–0.3% of the cases. Although the case-fatality rate of mumps encephalitis is low (1.4%), permanent sequelae such as deafness occur in about 25% of the cases. Acquired sensorineural deafness caused by mumps is one of the leading causes of deafness in childhood, affecting approximately 5 in 100 000 mumps patients.

Mumps orchitis occurs in 20%–50% of postpubertal males. Both testes are affected in approximately 20% of these cases, but mumps orchitis is rarely associated with permanently impaired fertility. However, a history of mumps orchitis seems to be a risk factor for testicular cancer.

Symptomatic oophoritis and mastitis are relatively uncommon, and apparently without long-lasting consequences for the patients. Acquisition of mumps during the first 12 weeks of pregnancy is associated with a high (25%) incidence of spontaneous abortions, although malformations following mumps virus infection during pregnancy have not been found.

Pancreatitis is reported as a complication in approximately 4% of the cases, but the relationship of mumps disease to diabetes mellitus remains speculative.

In the prevaccination era mumps used to be the main cause of viral encephalitis in the United States. According to Swedish estimates, before the introduction of routine vaccination, about 1000 annual cases of mumps meningitis required approximately 20 000 days of hospitalization and resulted in 20 000 to 40 000 days of disability. In countries where vaccines against mumps were introduced in the late 1960s, the incidence of this disease has dropped by 88% – 99%. Protection against mumps correlates with the presence of specific serum antibodies, which persist for more than 10 years following vaccination. However, with insufficient vaccination coverage resurgent outbreaks have occurred, as was the case in the United States between 1985 and 1987 when a fivefold increase in mumps incidence was recorded. The increase was accompanied by a shift in peak incidence from children aged five to nine years to children and adolescents aged 10–19 years. The largest increase was seen in the age group 15–19 years, which accounted for more than one-third of the reported total number of cases in this period. This resurgence was a consequence of low vaccine coverage in the cohort of children born between 1967 and 1977. There was no evidence of waning immunity in vaccinated persons.

Furthermore, the states that required proof of mumps immunity for school attendance had incidence rates only one-tenth of the states without such vaccination requirements, strongly suggesting that failure to vaccinate, rather than vaccine failure, was the prime reason for the observed epidemiological shift.

By the year 2000, approximately 120 countries or regions had included vaccination against mumps in their national immunization services, the vast majority combining mumps with measles and rubella vaccines (MMR). However, in the African Region only Egypt has included vaccination against mumps, and in the South-East Asia Region, only Singapore, Thailand and Brunei have done so. In these two regions mumps incidence remains high, with epidemic peaks every two to five years, mostly affecting children five to nine years of age.

The pathogen and disease

The mumps virus belongs to the family *Paramyxoviridae*. The average size of the spherical mumps virus is 200 nm. A host cell-derived lipid membrane encloses the nucleocapsid containing a single-stranded RNA genome. Embedded in the membrane are protruding glycoproteins such as hemagglutinin and neuraminidase. The viral (V) antigen is also associated with the membrane. Antibodies to the V antigen occur in late infection whereas antibodies to the nucleocapsid (the soluble (S) antigen) are detectable in early stages. Simple and reliable enzyme-linked immunosorbent assays (ELISAs) specific for antibodies to mumps virus are widely available.

Mumps virus replicates in a variety of cell cultures as well as in embryonated hens' eggs. For primary isolation in routine diagnostic virology, monkey kidney, human embryonic kidney or HeLa cell cultures are used. The presence of mumps virus in a cell culture may be detected by the Haemagglutination Inhibition Assay (HAI) test.

Humans are the only known natural host for mumps virus. The virus is spread via direct contact or by airborne droplets from the upper respiratory tract. It requires more intimate contact for transmission than the measles or varicella viruses. The incubation time averages 16–18 days with a range of two to four weeks. Typically, mumps begins with non-specific symptoms such as myalgia, headache, malaise and low-grade fever that within a day are followed by the characteristic unilateral or bilateral swelling of the parotid glands. Within one to three days, other salivary glands are visibly affected in approximately 10% of the cases. After about one week, fever and glandular swelling disappear, and unless complications occur, the illness resolves completely. In approximately 30% of the cases, infection passes with non-specific symptoms only or without symptoms at all. There is no specific therapy.

Protective immune response

Only one serotype of mumps virus exists. In general, natural infection confers lifelong protection against the virus, but recurrent mumps attacks have been reported. It is not known whether boosting by circulating wild virus in the community is a prerequisite for lifelong immunity against this disease. Clinically diagnosed mumps is regarded as evidence of immunity. Serological confirmation of immunity is based on the demonstration of specific serum IgG using common immunoassays. In immune individuals IgA antibodies secreted from the nasopharyngeal mucosa exhibit neutralizing activity against mumps virus and are regarded as a first-line defence.

Studies in several different countries have demonstrated that the seroprevalence of antibodies to mumps virus often reaches approximately 90% in individuals 14–15 years of age. Hence, in such populations, persons born 20 years or more before the implementation of large-scale childhood vaccination may be regarded as naturally immune. However, the adult seroprevalence may differ considerably between countries, and in some areas the protection rate may be as low as 50%. Low seroprevalences among the adult population may reflect real differences in transmission rates of mumps virus, a lengthy interval since the most recent outbreak, or differences in sampling or laboratory technique. Assumed susceptible persons may be vaccinated without preceding laboratory testing.

The justification for vaccine control

Although deaths due to mumps are rare, the disease can impose a substantial economic burden on society due to the fact that, in unvaccinated communities, almost every person may get infected and run a relatively high risk of complications.

Studies in industrialized countries have shown the incorporation of effective mumps vaccines into national immunization services to be highly cost-beneficial. In Austria, the benefit-cost ratio was 3.6 for routine childhood vaccination using the Jeryl Lynn mumps vaccine. In Israel, the benefit-cost ratio was 5.9 for routine immunization with MMR vaccine at 15 months of age. A South African study indicates that adding mumps (and rubella) vaccines to the measles vaccination programme may be very cost effective.

Generally, effective vaccines against mumps and high vaccination coverage may reduce the incidence of this disease to insignificant levels. For example, in Finland in 1996, mumps was eliminated following 14 years of programmatic vaccination. Accompanying surveillance revealed no persistent sequelae or deaths attributable to the vaccine. Furthermore, in spite of a few imported cases no secondary cases have been reported, indicating a sustained immunity in the community.

Mumps vaccine candidates

A killed mumps virus vaccine that was licensed in the United States in 1948 and used from 1950 to 1978, found little acceptance because it induced only short-term immunity of low protective efficacy. Since then, live, attenuated mumps virus vaccines have been developed in Japan, the Russian Federation, Switzerland and the United States. The vaccines are scheduled for either one or two doses, the first given at 12–15 months of age and the second at 9–12 years of age. They are available as monovalent, bivalent measles-mumps (MM) vaccines and trivalent measles-mumps-rubella (MMR) vaccines. WHO requirements do not specify the minimum amount of vaccine virus that one human dose should contain. Rather, this is determined by the national control authority of the country where the vaccine is produced. Most of these vaccines contain more than 1000 cell-culture infective doses of attenuated mumps virus per dose. Sorbitol and hydrolysed gelatine are used as stabilisers and neomycin is added as a preservative to the mumps vaccines. The vaccines are cold-chain-dependent, and need to be protected from light both before and after reconstitution. Reconstituted vaccine must be discarded if it is not used within eight hours.

Different attenuated strains of mumps virus are used for the development of live vaccine. After its introduction in the United States in 1967, the Jeryl Lynn strain was recommended for routine use in 1977. The vaccine was developed by passaging the virus in embryonated hens' eggs, then in chick embryo cell cultures. By 1992, it had been administered to approximately 135 million children and adults around the world. In 1995, the number of reported mumps cases in the United States was only about 1% of the 1968 figures. Studies in industrialized countries show that a single dose of the Jeryl Lynn strain mumps vaccine leads to seroconversion rates of 80%–100%. Children given one dose of the MMR vaccine containing the Jeryl Lynn component are in 73% of the cases still seropositive after 10.5 years. Similarly, following a two-dose schedule administered five years apart, 86% are seropositive four years after the second dose. Outbreak-based studies from the United States have demonstrated that the protective efficacy of the Jeryl Lynn strain against clinical mumps ranges from 75% to 91%. However, the risk of mumps seemed to increase with the number of years following vaccination, suggesting some waning of protective immunity.

The incidence of vaccine-associated cases of aseptic meningitis ranges from 0.1–1 per 100 000 doses of the Jeryl Lynn mumps vaccine.

The Leningrad-3 vaccine strain developed in the former Soviet Union is propagated in guinea-pig kidney cell culture and further passaged in Japanese quail embryo culture. Approximately 8–11 million doses are produced annually. This vaccine has achieved seroconversion rates of 89%–98% in children one to seven years of age and protective efficacy ranging from 92% to 99%. Furthermore, a trial involving 113 967 children aged 1–12 years, demonstrated 96.6% protective efficacy when used as urgent prophylaxis during a Russian mumps outbreak. The outbreak was arrested within one month, and a clear positive economic effect was demonstrated.

Passive surveillance and retrospective reviews indicate an incidence of 20–100 cases of aseptic meningitis per 100 000 doses of MM vaccine based on the Leningrad-3 strain.

The Leningrad-3 strain has been further attenuated in Croatia by adaptation to chick embryo fibroblast cell culture. The new strain designated L-Zagreb is used in Croatia, India and Slovenia. Studies of L-Zagreb in Croatia revealed protective properties equivalent to those seen with the Leningrad-3 strain and also the incidence of vaccine associated aseptic meningitis remained largely the same (2–90 per 100 000 doses of MMR).

Live mumps vaccine based on the Urabe strain was first licensed in Japan and then in France, Belgium and Italy. The Urabe strain is produced either in the amnion of embryonated hens' eggs or in chick embryo cell cultures. It has been used successfully in several countries and since 1979 more than 60 million persons have received this vaccine. Seroconversion rates in children aged 12–20 months range from 92%–100%, and in children nine months of age the corresponding range is 75%–99%. A comparative study in the United Kingdom using either the Jeryl Lynn or the Urabe strain in combination with measles and rubella vaccines showed that four years after a single dose of MMR vaccine the seropositivity rates were 85% for the Urabe strain and 81% for the Jeryl Lynn strain. In Canada, the corresponding rates five to six years after a single dose MMR vaccine were 93% and 85% respectively. A possible association of the Urabe strain with vaccine-induced meningitis has resulted in its withdrawal from some countries. Studies up to 1993 identified an incidence of approximately 100 cases of aseptic meningitis per 100 000 doses of MMR containing the Urabe mumps strain. However, the rates differed by manufacturer.

The Rubini strain was first licensed in Switzerland in 1985. It was developed by passage in a human diploid cell line, serial passaging in embryonated hens' eggs and then adapted to the MRC-5 human diploid cell line. Recent observations with the vaccine based on the Rubini strain suggest that this vaccine has lower efficacy than those based on the Jeryl Lynn or Urabe strains. A three-year study in Switzerland showed that the Rubini strain conferred only 6.3% protection whereas the Urabe and Jeryl Lynn based vaccines achieved 73.1% and 61.6% efficacy respectively. In another study the corresponding figures were 12.4%, 75.8% and 64.7%. An explanation for these poor results may be the high number of passages (>30) resulting in an overly attenuated vaccine strain. Furthermore, the manufacturer of the Rubini strain vaccine now recommends a second dose at four to six years of age. Data on the protective efficacy of this schedule are currently not available.

Attenuated mumps virus strains that are used on a limited scale only include the Hoshino, Torii and NKM-46 strains. They are reported to possess immunogenic properties similar to the Urabe strain.

Adverse reactions

In general, adverse reactions to mumps vaccination are rare and mild. However, moderate fever may occur rarely and aseptic meningitis has been reported in 0.1–100 per 100 000 vaccinees, depending on the vaccine strain used. Vaccine-associated meningitis resolves spontaneously in less than one week without any sequelae.

Contraindications

There are few contraindications to mumps vaccination. As with all live attenuated vaccines, mumps vaccine should not be administered to individuals with advanced immune deficiency or immunosuppression. Pregnant women should not receive mumps vaccine, and pregnancy should be avoided for three months after vaccination (fetal damage has, however, not been documented). Allergy to vaccine components such as neomycin and gelatine is contraindicative.

WHO position on mumps vaccines

Although the currently available mumps vaccines are of variable quality in terms of adverse reactions and protective efficacy, there is ample evidence that the best of these vaccines are highly efficacious and safe. Where included in successful national immunization services, these vaccines have led to dramatic reductions in the incidence of mumps. Furthermore, primary mumps vaccination is easily adapted to the national vaccination programmes, and does not interfere significantly with simultaneously administered vaccines, for example the recommended combination with rubella and measles-containing vaccines. On the other hand, live vaccines' dependency on cold-chain conditions is a disadvantage for their use, particularly in low-income countries with hot climates.

In view of the moderate morbidity and the low mortality of this disease, its socioeconomic impact is essential when deciding on the priority of mumps vaccination in national immunization services. Assessment of that impact requires careful evaluation of disease burden and costs associated with purchase of the vaccine and vaccination, including the economic impact of possible adverse effects.

Countries considering inclusion of mumps vaccination into their national immunization service should be able to offer the vaccine to all children aged 12–15 months. The addition of mumps vaccine to the measles vaccination programme, using the MM or MMR combined vaccines is logistically sound and will increase the benefit-cost ratio. The MMR combination is strongly encouraged where it is affordable.

Serological studies show that vaccine response rates are excellent from the age of 12 months and, for the Urabe vaccine strain, high titres are achieved from the age of 9 months. When aiming at mumps control MMR vaccination at 9–15 months of age and coverage rates of 80% or more would be appropriate. Coverage rates below 70%–80% may result in an epidemiological shift. This because reduced, but not interrupted, circulation of mumps virus in the community is likely to leave a large proportion of adults without immunity from natural infection. Therefore, if only a relatively low coverage can be achieved, the introduction of a second vaccine dose at the age of 9–12 years should be considered. If a large proportion of the population remains seronegative for mumps, the vaccine may be provided to adults at special risk, such as health workers, teachers and military personnel.

High-quality mumps vaccines generally confer substantial protection and will reduce the costs associated with patient care and lost working days due to mumps. WHO therefore recommends the use of such vaccines in all countries with well-functioning childhood vaccination programmes, provided that sustained high-level coverage is afforded and that reduction of mumps is a public health priority.

Mumps vaccination should be followed by registration of immunization coverage. In order to reduce underestimation by passive surveillance, mumps should be made a notifiable disease.

Public health strategies

Mumps, a generalized infection caused by a virus of the *Paramyxovirus* family, primarily affects the salivary glands, causing parotitis. Although mostly responsible for a mild childhood disease, this virus may also affect adults, among whom complications such as orchitis are relatively common. Meningitis, encephalitis and permanent neurological sequelae are rare complications of mumps at any age. In most parts of the world the annual incidence of mumps is in the range 100–1000 per 100 000 population, and epidemics occur at intervals of two to five years. The incidence of the disease peaks among children aged five to nine years. Natural infection with mumps virus is thought to confer lifelong protection. Theoretically, the disease could be eradicated, but public health efforts to control it are given low priority. Many countries have chosen to limit its effects by immunizing populations of children. This is particularly important in reducing the disease acquired in adulthood, when the complications may be comparatively severe.

WHO perspective

The currently available mumps vaccines vary in their protective efficacy and the adverse reactions they induce but there is ample evidence that most of them are highly effective and safe. Primary mumps immunization can easily be incorporated into successful national immunization services, where these vaccines have led to dramatic reductions in the incidence of the disease.

All the commercially available mumps vaccines are based on live attenuated strains of the virus. So far, approximately 500 million doses of mumps vaccine have been administered, mainly in the industrialized world. In 2002, 118 countries or territories reported using mumps vaccine in their national immunization services, mainly in combination with measles and rubella vaccines.

The introduction of mumps vaccine should be considered only in countries that have established, or are in the process of establishing, adequate programmes for the elimination of measles and the control of congenital rubella syndrome. This is because WHO accords the latter objectives a higher priority than mumps control. In such countries the combination of mumps vaccine with measles and rubella vaccines is recommended. National decisions to implement large-scale mumps immunization should be based on careful cost-benefit analyses, including the comparative analysis of mumps control versus the control of other vaccine-preventable diseases in the countries concerned.

Mumps vaccines are available as monovalent, bivalent measles–mumps (MM) and trivalent measles–mumps–rubella (MMR) vaccines. WHO does not specify the minimum amount of vaccine virus that one human dose should contain. This is determined by the national regulatory authority of the country where the vaccine is produced. The vaccine requires an effective cold chain for transportation and must be protected from light both before and after reconstitution. Reconstituted vaccine that remains unused for six hours must be discarded.

Countries considering the inclusion of mumps vaccine in their national immunization services should set targets for elimination or control and should design their immunization strategies accordingly.

Special issues

Mumps control: The control of mumps can be achieved through high routine coverage with an effective mumps-containing vaccine administered at 12–18 months of age. Children immunized with most mumps vaccines at the age of 12 months or older have excellent serological response rates. Programmes should aim at infant coverage of more than 90%. Low immunization coverage may reduce the number of cases in infants but fails to interrupt circulation of the mumps virus in the community. Furthermore, there is an associated epidemiological shift, involving a paradoxical increase in the number of cases in adults who are without immunity from natural infection. The addition of mumps vaccine to the measles vaccination service by using the MMR combined vaccine is logistically sound. The use of the MMR combination is strongly encouraged where it is epidemiologically indicated and affordable.

Mumps elimination: Strategies for achieving mumps elimination should include:

- Achieving high (more than 90%) coverage with a first dose of mumps-containing vaccine at the age of 12–18 months;
- Ensuring a second opportunity for immunization;
- Conducting catch-up immunization of susceptible cohorts.

A second opportunity is not required in countries where coverage with the first dose is sufficiently high (i.e. more than 90%). If a second opportunity is needed it can be given by administering a second routine dose or by conducting periodic catch-up campaigns. If an initial catch-up campaign is implemented, the target age group should be that in which susceptibility to mumps is highest. In most unvaccinated populations a majority of children acquire mumps infections before reaching the age of 10 years.

Reactogenicity and immunogenicity: In general, adverse reactions to mumps vaccine are rare and mild. The most common adverse reactions are parotitis and low-grade fever. However, moderate fever sometimes occurs and aseptic meningitis has been reported at widely different frequencies. Countries intending to use mumps vaccine during mass campaigns should give special attention to planning. The mumps vaccine strain should be carefully selected, health workers should be trained on expected rates of adverse events following immunization, guidelines should be provided on the monitoring, investigation and management of such events, and community advocacy and health education should be carried out. Because meningitis may occur

as an adverse event during mass campaigns, particular care must be exercised in selecting a suitable vaccine strain that has low meningitis reaction rates. Most licensed mumps vaccine strains are highly efficacious. High seroconversion rates after immunization have been reported. In contrast, the Rubini strain exhibits low seroconversion and effectiveness rates and is not recommended by WHO for use in national immunization services.

This chapter was last published as a position paper: Mumps virus vaccines. WHO position paper. *Weekly Epidemiological Record,* 2001, 76:346–355 and is available on the Internet at http://www.who.int/wer/pdf/2001/wer7645.pdf.

Administration summary

Type of vaccine	Live attenuated viral
Number of doses	One dose given subcutaneously, usually in MMR
Schedule	As for measles vaccine
Booster	True booster not required
Contraindications	Advanced immune deficiency or immunosuppression; allergy to vaccine components such as neomycin and gelatin; avoid in pregnancy, although fetal damage has not been documented when given in pregnancy
Adverse reactions	Parotitis and low-grade fever, rarely moderate fever; aseptic meningitis may occur at widely different frequencies
Special precautions	None

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Pertussis vaccine

Summary and conclusions

Pertussis (whooping cough) is a highly contagious disease caused by *Bordetella pertussis.* Worldwide, this bacterial agent causes some 20–40 million cases of pertussis and an estimated 200 000–400 000 fatalities each year. Although pertussis may occur at any age, most cases of serious disease and the majority of fatalities are observed in early infancy. Vaccines are the most rational approach to pertussis control. For several decades inactivated whole cell vaccines (wP) have been part of national childhood vaccination programmes, dramatically reducing the considerable public health impact of pertussis. These vaccines are currently being produced in over 40 countries, including many developing countries. Currently, worldwide pertussis vaccination coverage is about 80%. Frequent (but usually mild) adverse reactions and a fear of rare but serious acute or chronic neurological events associated with wP vaccination have prompted the development of a new generation of pertussis vaccines, the acellular (aP) vaccines. However, despite thorough investigations, the link suspected between wP vaccines and rare cases of permanent neurological damage has not been confirmed. The aP vaccines, which contain one to five different components of *B. pertussis,* have proved to be efficacious, although more expensive, and to compare favourably with wP vaccines in terms of common adverse effects. They are now licensed in several countries. At their most effective, aP and wP vaccines share similar efficacies. Both wP and aP are usually administered in combination with diphtheria and tetanus toxoids (DTwP or DTaP).

For more than four decades, use of wP of documented quality in infant immunization services has been highly effective in preventing pertussis all over the world.

- wP vaccines are considerably less costly than the aP vaccines. Therefore, in most countries, wP vaccines remain the appropriate choice for public health immunization services.
- While in terms of severe adverse effects aP and wP vaccines appear to have the same high level of safety, mild to moderate adverse reactions are less commonly associated with the aP vaccines.
- Similar high efficacy levels are obtained with the best aP and wP vaccines, but the level of efficacy may vary considerably between the vaccines within these two groups. Reliable comparisons of different aP and wP vaccines or between aP and wP vaccines, are possible only in studies that are carefully designed for that purpose. So far, no trial has had the optimal design to adequately compare different candidate antigens and the choice and number of antigen components of the ideal aP vaccine is still debated.

- WHO endorses the use of aP vaccines of documented quality in countries where pertussis vaccination is not widely accepted because of the reactogenicity of wP.
- The main impediments to wider use of the aP vaccines are their high price and concern about their duration of protection. If these issues can be satisfactorily resolved, widespread use of this product will be encouraged in the long term.
- Areas in need of further research include the duration of protection following primary immunization with wP or aP vaccines, interference between aP and other vaccines when used in combination, ability of aP to induce a herd effect, and the epidemiology of pertussis in the adult population.

Public health impact

Some 20–40 million cases of pertussis occur worldwide each year, 90% of which are found in developing countries. About 200 000–400 000 of these patients, mostly infants, die from the disease. In its early catarrhal stage pertussis is highly communicable, with a secondary attack rate of up to 90% among non-immune household contacts. Untreated patients may be contagious for three weeks or more following the onset of typical coughing attacks, although communicability diminishes rapidly after the catarrhal stage. Pertussis occurs mostly in infants and young children, and severe disease and death are reported mainly in infancy. In the youngest infants, periods of apnoea may follow the coughing spasms. Pneumonia is a relatively common complication; seizures and encephalopathy occur more rarely. The incidence of pertussis in older children and adults varies with the frequency of exposure to *B. pertussis* and vaccination coverage in the population. In Western countries about 10%–12% of all cases have been reported in persons more than 15 years of age. However, reliable incidence data are scarce, as atypical clinical courses and unrecognized infection are common in these age groups. In addition, laboratory confirmation of suspected cases is mostly unavailable. Asymptomatic carriers of *B. pertussis* seem to be rare among children, and although adolescents and adults are considered to be an important source of infection, the carrier rates in these age groups are largely unknown.

Currently, approximately 80% of the world's children are vaccinated against pertussis, most of whom have received the DTwP combination which has been strongly promoted by EPI. By 1997, vaccination had reduced the pertussis-specific mortality to about 400 000 among children under five years of age in developing countries, preventing about 750 000 deaths.

Immunization with wP vaccines is frequently (1 in 2–10 injections) associated with minor adverse reactions such as local redness and swelling, fever and agitation. Prolonged crying and seizures are less common (fewer than 1 in 100) whereas hypotonic-hyporesponsive episodes are rare (fewer than 1 in 2000). Acute encephalopathy can also occur in temporal association with wP immunization, but very rarely (fewer than 1 in 10.5 million). In the 1970s, safety issues led to reduced professional and public acceptance of this vaccine, and in a few industrialized countries the wP vaccine was even excluded from the national immunization services with a dramatic increase in pertussis cases. In recent years, upon the introduction of the aP vaccine, some of these countries have returned to the DTP combination, replacing wP by aP vaccines.

The national childhood encephalopathy study in the United Kingdom showed a small increased risk of acute encephalopathy (primarily seizures) following DTP immunization. However, subsequent detailed reviews of all available studies by a number of groups (including the United States Institute of Medicine, the Advisory Committee on Immunization Practices, and the paediatric associations of Australia, Canada, the United Kingdom and the United States) concluded that the data did not demonstrate a causal relationship between DTwP and chronic nervous system dysfunction in children. Thus, although febrile seizures and hypotonic-hyporesponsive episodes that may follow DTwP are disturbing to parents and physicians alike, there is no scientific evidence that these reactions have any permanent consequences for the children.

The pathogen

Bordetella pertussis, the causative agent of pertussis, is a Gram-negative rod with affinity to the mucosal layers of the human respiratory tract. Significant antigenic variation has not been demonstrated. *B. pertussis* is a pathogen for humans only. The infection is easily transmitted by close contact, mainly through droplets. In addition to the pertussis toxin, the virulence factors include filamentous haemagglutinin, fimbriae and pertactin. Following an incubation period of 7–10 days, susceptible individuals develop catarrhal symptoms including cough, which in typical cases gradually develops into whooping paroxysms. During the paroxysmal phase of the disease, eradication of the bacteria by antimicrobial drugs, such as erythromycin, will not significantly change the clinical course. So far, development of increased resistance to relevant antimicrobial drugs seems to be very uncommon. Bacteriological confirmation of suspected whooping cough is often missed, as culturable *B. pertussis* does not seem to persist far beyond the catarrhal stage, and in addition requires special growth factors to grow on artificial media. A mild, pertussis-like disease in humans is sometimes caused by the closely related agent *B. parapertussis.*

Immune response

Pertussis results in long-lasting but not necessarily lifelong protection against the typical clinical manifestations of the disease. However, the protection may not be complete, as atypical or unrecognized infection in presumably immune persons, particularly adults, may be easily overlooked. Also, newborn babies of mothers who have had pertussis are not necessarily protected. Hence, following previous infection, occasional exposure to *B. pertussis* strains circulating in the community may be required to sustain high-level immunity. Although the level of antibodies to pertussis toxin or to the filamentous haemagglutinin are sometimes used as serological indicators of protection, lack of generally accepted correlates of immunity and animal models are impediments to the evaluation of new pertussis vaccine candidates and the monitoring of the consistency of production.

Justification for vaccine control

Before the worldwide introduction of pertussis vaccine into the routine childhood vaccination programmes, pertussis was of considerable public health concern in developed as well as in developing countries. Due to the highly contagious nature of the disease, there are always a large number of secondary cases among non-immune contacts. Although prophylactic antibiotic treatment in the early incubation period usually prevents disease, the difficulty of early diagnosis and the costs involved and the inherent ecological concerns related to induction of drug resistance, limit prophylactic treatment to selected individual contacts.

Whole-cell pertussis vaccines

Immunization of infants with wP vaccines in approved schedules, usually in combination with D and T, has shown an efficacy of 80% or more, and in countries with good vaccination coverage, morbidity and mortality from pertussis have been reduced to low levels. However, in recent years an increase in the incidence of pertussis, particularly in older children and adults, has been reported from a number of countries including Australia, Canada, the United States and several countries in Europe. The reasons for this increase are largely unknown, but sub-optimal quality of the involved wP vaccine and cyclic variation in disease patterns may have added to the effect of waning vaccine-derived immunity in certain countries. Whereas failure to maintain high primary immunization coverage regularly results in increasing pertussis morbidity and mortality, particularly in the youngest age group, other mechanisms are likely to explain an increase in reported morbidity in older age groups, including improved surveillance and increased recognition of the problem. Thus, if occasional exposure to *B. pertussis* serves to sustain vaccine-induced immunity, it is conceivable that increased morbidity from pertussis will occur among older children and adults in communities where such exposure is reduced below a critical level.

Whole-cell pertussis vaccines of known good quality are readily available and cost only a few US cents per dose in developing countries. Furthermore, several developing countries are producing wP vaccines sufficient for their national needs. The impact of switching to aP production or continuing to produce wP should be carefully studied by these countries in the light of their long-term plans. Cost-effectiveness studies on internationally licensed wP vaccines have clearly documented their value in industrialized countries.

Concern about safety of the wP vaccine has made routine pertussis vaccination of infants quite controversial in some countries, and led to the development of a new generation of pertussis vaccines based on selected bacterial components, rather than on inactivated whole cells.

Acellular pertussis vaccines

The first aP vaccines were developed in Japan, where such vaccines were licensed for immunization of children aged two years or more in 1981, and for infants from the age of three months in 1989. The first DTaP combination was licensed in the United States in 1991, at first as an alternative to DTwP boosters in children who had received their basic DTwP series. Vaccination with aP, starting at the age of two months, with or without the DT toxoids, is now included in routine childhood vaccination programmes in several countries. It is not known whether the duration of protection with aP vaccines is the same as with wP vaccines.

Decreased reactogenicity of aP vaccines is likely to improve public acceptance of pertussis vaccination, thereby having a positive impact on public attitudes towards childhood vaccination in general. In addition, the decreased reactogenicity of these products encourages consideration of the utility of booster doses later in life.

The most effective wP and aP vaccines show similar efficacy in preventing typical pertussis. All aP vaccines contain inactivated pertussis toxin, which in most cases is combined with filamentous haemagglutinin and sometimes additional *B. pertussis* components such as fimbrial antigens and pertactin. In large multicentre studies recently performed in Germany, Italy and Sweden, the DTaP vaccines proved to be significantly less reactogenic than the DTwP vaccines in terms of high fever, seizures and hypotonic-hyporesponsiveness episodes. Differences in study design, vaccine preparation and study populations complicate direct comparison within the group of aP vaccines as well as between aP and wP vaccines. A number of aP vaccines are now available, either as individual vaccines or DTaP combinations, with or without the addition of hepatitis B, Hib, or poliovirus vaccine (IPV). Contraindications to DTaP are likely to be very rare. As with DTwP, HIV-infected infants should receive the vaccine. In addition to use in primary infant series, the less reactogenic aP vaccines should improve recruitment to the fourth and fifth doses at two years (18–24 months) and four to seven years of age, where recommended.

WHO position on pertussis vaccines

There are major differences in the contents, mode of preparation and efficacy of wP and aP vaccines. However, comprehensive clinical trials have demonstrated that the most efficacious vaccines of either category will protect more than 80% of the recipients from clinical disease. Provided that high and sustained vaccination coverage is achieved, such vaccines will eliminate pertussis as a public health problem. At the same time, recent experience illustrates the importance of ensuring the use of documented high-quality wP vaccines in national immunization services.

No causal link has been identified between wP or aP vaccination and permanent brain damage or death. In terms of redness and swelling at the site of injection, fever, agitation, prolonged crying, febrile seizures and hypotonic-hyporesponsive episodes, aP vaccines show some improvement compared with wP vaccines. Better information on the frequency (if any) of rare, serious reactions will be obtained with widespread aP use and post-marketing safety studies.

There is no indication of clinically significant immunological interference between aP and other vaccines simultaneously administered at different sites. However, the reduced immunogenicity of Hib vaccine when combined with some aP vaccines is of concern and needs further elucidation.

Little is known concerning the duration of protection of aP and wP vaccines in populations without intercurrent pertussis infections and *B. pertussis* carriage. Similarly, the possible effect of the respective vaccines on pharyngeal colonization of *B. pertussis* and on mild pertussis among adolescents and adults needs to be better established, considering the possible role of young adults in the epidemiology of the disease. Enhanced surveillance is required to assess the true long-term protection provided by wP as well as aP vaccines.

Although most comparative studies between aP and wP have so far been conducted in industrialized countries, in principle the new DTaP vaccines are expected to be fully effective in all regions of the world. However, the considerably higher development costs of aP as compared with wP vaccines result in prices per dose that are unlikely to be currently affordable for most developing countries. On the other hand, in those countries where the wP component of the DTP combination was excluded for fear of serious side-effects, aP may be a prerequisite for popular acceptance of pertussis vaccination as part of the childhood vaccination programme.

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Administration summary

Type of vaccine	Inactivated whole cell wP or acellular aP [1]
Number of doses	At least three primary doses, given by the intramuscular route, combined with diphtheria and tetanus toxoid
Schedule	6, 10, 14 weeks of age [2]
Booster	DTP at 18 months to 6 years of age [3]
Contraindications	Severe anaphylactic reaction to previous dose or to any constituent
Adverse reactions	Mild local or systemic reactions are common
Special precautions	–

[1] wP and aP can be combined in a quadrivalent or pentavalent presentation with D, T, HBV and Hib vaccines.

[2] There is considerable variation between different national immunization schedules in the timing of the three primary doses.

[3] WHO recommends that, where resources permit, an additional dose of DTP be given after completion of the primary doses. However, the need and timing for additional booster doses of DTP or should be addressed by individual national programmes.

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Pneumococcal vaccines

Summary and conclusions

Pneumococcal diseases are a major public health problem all over the world. The etiological agent, *Streptococcus pneumoniae* (the pneumococcus) is surrounded by a polysaccharide capsule. Differences in the composition of this capsule permit serological differentiation between about 90 capsular types, some of which are frequently associated with pneumococcal disease, others rarely. Invasive pneumococcal infections include pneumonia, meningitis and febrile bacteremia; among the common non-invasive manifestations are otitis media, sinusitis and bronchitis. At least 1 million children die of pneumococcal disease every year, most of these being young children in developing countries. In the developed world, elderly persons carry the major disease burden. Conditions associated with increased risk of serious pneumococcal disease include HIV infection, sickle-cell anaemia and a variety of chronic organ failures. Vaccination is the only available tool to prevent pneumococcal disease. The recent development of widespread microbial resistance to essential antibiotics underlines the urgent need for more efficient pneumococcal vaccines.

Immunity following pneumococcal disease is directed primarily against the capsular serotype involved. The currently licensed pneumococcal vaccine is based on the 23 most common serotypes, against which the vaccine has an overall protective efficacy of about 60%–70%. Children under two years of age, and persons suffering from various states of immunodeficiency, for example HIV infection, do not consistently develop immunity following vaccination, thus reducing the protective value of the vaccine in some major target groups for pneumococcal disease. However, in a healthy elderly population the polysaccharide vaccine provides relatively efficient protection against invasive pneumococcal disease.

Extensive clinical trials are now under way with a new generation of pneumococcal vaccines. These protein-polysaccharide combinations, known as conjugate vaccines, contain 7–11 selected polysaccharides bound to a protein carrier, and induce a T-cell dependent immune response. These vaccines are likely to be protective even in children under two years of age, and may reduce pneumococcal transmission through a herd effect.

The currently licensed pneumococcal polysaccharide vaccine has been shown to protect adults and children under two years of age against invasive pneumococcal infection, and its use is recommended for adults and children at high risk of pneumococcal disease. Such groups include splenectomized patients and persons with chronic organ failure or sickle-cell disease, and the elderly population.

HIV-infected persons are at high risk of invasive pneumococcal disease. The protective efficacy of the vaccine in this population is currently being evaluated. The use of the vaccine in children under two years of age and pregnant women remains controversial and requires further study.

Due to reduced immunogenicity and unclear efficacy in children under two years of age, the current polysaccharide vaccine is not recommended for routine immunization of children in this age group. Unfortunately, this excludes the most important target group for pneumococcal vaccines, namely the youngest children in developing countries.

In view of the potential public health impact of successful vaccines against pneumococcal disease, WHO considers the development of safe, efficient and appropriately priced pneumococcal conjugate vaccines a matter of the highest priority. Detailed planning for their use is possible only when the results of protective efficacy trials are available. In the meantime, more information on the epidemiology and burden of pneumococcal disease is urgently required, in particular from developing countries.

Background

Infections caused by pneumococci are a major cause of morbidity and mortality all over the world. Pneumonia, febrile bacteraemia and meningitis are the most common manifestations of invasive pneumococcal disease, whereas bacterial spread within the respiratory tract may result in middle-ear infection, sinusitis or recurrent bronchitis. Compared with invasive disease, the non-invasive manifestations are usually less severe, but considerably more common. Thus, in the United States alone, 7 million cases of otitis media are attributed to pneumococci each year. Although all age groups may be affected, the highest rate of pneumococcal disease occurs in young children and in the elderly population. In addition, persons suffering from a wide range of chronic conditions and immune deficiencies are at increased risk. In developing countries infants under three months of age are at particularly high risk, especially for pneumococcal meningitis.

In spite of the importance of pneumococcal disease, there is a scarcity of information on disease burden, particularly from developing countries. This is partly due to the inherent problem of obtaining an etiological diagnosis in cases of pneumonia. However, based on available data, acute respiratory infections kill an estimated 2.6 million children under five years of age annually. The pneumococcus causes over 1 million of these deaths, most of which occur in developing countries, where the pneumococcus is probably the most important pathogen of early infancy. In Europe and the United States, pneumococcal pneumonia is the most common community-acquired bacterial pneumonia, estimated to affect approximately 100 per 100 000 adults each year. The corresponding figures for febrile bacteraemia and meningitis are 15–19 per 100 000 and 1–2 per 100 000, respectively. The risk for one or more of these manifestations is much higher in infants and elderly people. Even in economically developed regions, invasive pneumococcal disease carries high mortality; for adults with pneumococcal pneumonia the mortality rate averages 10%–20%, whilst it may exceed 50% in the high-risk groups. Pneumonia is by far the most common cause of pneumococcal death worldwide.

The pathogen

Streptococcus pneumoniae is a Gram-positive encapsulated coccus. Based on differences in the composition of the polysaccharide capsule, about 90 serotypes are identified. This capsule is an essential virulence factor. The majority of pneumococcal disease in infants is associated with a small number of these serotypes, which may vary by region. Current data suggest that the 11 most common serotypes cause at least 75% of invasive disease in all regions. Pneumococci are transmitted by direct contact with respiratory secretions from patients and healthy carriers. Although transient nasopharyngeal colonization rather than disease is the normal outcome of exposure to pneumococci, bacterial spread to the sinuses or the middle ear, or bacteraemia following penetration of the mucosal layer, may occur in persons susceptible to the involved serotype. Pneumococcal resistance to essential antimicrobials such as penicillins, cephalosporins and macrolides is a serious and rapidly increasing problem worldwide. Facilities for laboratory diagnosis of *S. pneumoniae,* based on growth in traditional culture media, are available in laboratories for routine clinical microbiology, whereas serotyping is performed only in reference laboratories.

Protective immune response

Protective immunity is mainly dependent upon type-specific, anticapsular antibodies, although serological correlates of immunity are poorly defined. The polysaccharide capsule antigens do not regularly elicit protective levels of antibodies in children under two years of age, and in individuals with advanced immunological impairments. Furthermore, the polysaccharides do not induce immunological memory, which is required for subsequent booster responses. The spectrum of prevailing capsular types varies with age, time and geographical region, although common serotypes are consistently identified throughout the world. The currently licensed polyvalent pneumococcal vaccine contains antigens from 23 of the serotypes that most commonly cause invasive disease worldwide.

Justification for vaccine control of pneumococcal disease

Pneumococcal disease leads to a wide range of important human pathologies, from common upper respiratory tract infections to severe invasive manifestations such as pneumonia, meningitis and septicemia, and is a major public health problem all over the world. In developed countries this disease burden is carried mainly by the elderly population; in developing countries mostly by the youngest children. With increasing sophistication of life-saving medical technology, and with increasing life expectancy, pneumococcal disease is becoming more common, and more costly to society. Except for vaccines, no public health measures are likely to have any significant impact on the incidence of this disease. Increasing pneumococcal resistance to essential antimicrobial drugs, and the ease with which resistant strains are spread all over the world, underline the importance of control through vaccination.

The currently available polyvalent pneumococcal vaccine has an average protective efficacy for the serotypes included of about 60%–70%. This vaccine is of documented value for protection against invasive pneumococcal disease in immunocompetent elderly people living in institutions, as well as in asplenic and sickle-cell patients.

At least in the United States the cost-effectiveness of a widespread vaccination programme for patients having had pneumonia, at risk of developing pneumonia, or aged 65 years and above, has been documented. However, the duration of protection in elderly and immunocompromised target groups is relatively short. Infants respond poorly to this vaccine. Also, the vaccine has no significant effect on nasopharyngeal carriage, and hence induces no herd effect. These important shortcomings underline the need for developing improved pneumococcal vaccines.

Conjugate pneumococcal vaccines are now undergoing clinical trials in various parts of the world, and the first phase III trial in the United States with one of these vaccines showed a high degree of efficacy against invasive pneumococcal disease (defined as blood or CSF culture-positive cases). It is likely that conjugate vaccines will overcome most of the problems inherent in the polysaccharide vaccine. As compared with the polysaccharide vaccine, the conjugate vaccines have a greater potential to control pneumococcal disease, regardless of age, including control of the serotypes most commonly responsible for resistance against multiple antimicrobials.

Pneumococcal vaccines

(i) The currently licensed vaccine

The polyvalent polysaccharide vaccine contains per dose (0.5 ml) 25 micrograms of purified capsular polysaccharide from each of the 23 capsular types of *S. pneumoniae* that together account for most cases (90%) of serious pneumococcal disease in Western industrialized countries. The marketed versions of this vaccine are almost identical. Relatively good antibody responses (60%–70%) are elicited in most healthy adults during the two to three weeks following a single intramuscular or subcutaneous dose of this vaccine. The immune response is unreliable in children under two years of age, and in immunocompromised individuals. Following the vaccination of pregnant women, antibodies are transferred both via the placenta and in the breast milk. However, it is not yet documented that maternal vaccination actually protects newborn infants against pneumococcal disease.

The polyvalent polysaccharide vaccine is recommended for selected groups under two years of age with increased risk of pneumococcal disease. Such groups include healthy elderly people (more than 65 years of age), particularly those living in institutions, and patients suffering from chronic organ failure, diabetes or certain immunodeficiencies. The vaccine has little protective efficacy in some important high-risk groups for pneumococcal disease, such as persons suffering from recurrent otitis media, haematological malignancies or chronic alcoholism. Revaccination after three to six years may be considered in certain high-risk groups such as patients with asplenia or nephrotic syndrome, where immunity following vaccination is known to decline rapidly.

Adverse reactions include some soreness at the site of injection and, more rarely, low-grade fever. Revaccination within less than three years may cause these reactions to become more severe, and is therefore not recommended in immunocompetent persons.

(ii) Candidate pneumococcal vaccines

Several manufacturers are in the process of developing pneumococcal vaccines based on the conjugation of selected capsular polysaccharides to a protein carrier, such as a bacterial toxoid. The protein carriers induce a T-cell dependent immune response to the polysaccharides, leading to immunological memory and boosting upon repeated injection. As the current polysaccharide vaccines may also be used to boost the response to the conjugates, the combined use of these vaccines may be a future cost-saving option. The conjugate vaccines that are currently in advanced stages of development contain 7–11 capsular serotypes, representing the most common causes of invasive pneumococcal disease in children. Significant immunological competition between the antigens included has not been observed. As with polysaccharide vaccines, the conjugate vaccines induce protection only against the serotypes involved; however, higher antibody levels are achieved, and the conjugates elicit an immune response more efficiently in infants and in immunodeficient persons. Several candidate conjugate vaccines have successfully passed the development phases dealing with safety and immunogenicity, and results from the first efficacy trial of a conjugate vaccine in infants show excellent protection against invasive disease. Looked at in comparison with the Hib vaccines, pneumococcal conjugate vaccines have been shown not only to protect against invasive disease, but also to suppress nasopharyngeal carriage of the pathogen. Therefore, these vaccines could possibly prevent even non-invasive pneumococcal disease and reduce bacterial transmission in the community. Such a herd effect would add considerable value to the conjugate vaccines.

At least theoretically, there is a possibility that large-scale use of the conjugate vaccines may result in a shift in prevailing serotypes from those affected by the vaccines to currently less prevalent serotypes. This possibility deserves careful observation, and is one of the reasons why alternative strategies to the development of a pneumococcal vaccine, such as the common protein antigen approach, should be actively pursued. Theoretically, such common antigens could induce universal protection against pneumococcal disease, regardless of the serotype involved.

WHO position on pneumococcal vaccines

(i) The polysaccharide vaccine

The safety of the current polysaccharide vaccines in older children and non-pregnant adults is well documented. In developed countries they have proved effective against serious pneumococcal disease in children under two years of age, and in some of the adult and elderly populations known to be at particular risk from this disease. The main indications for use of the polysaccharide vaccines are:

- The protection of healthy elderly people, particularly those living in institutions;
- Patients with chronic organ failure;
- Particular immunodeficiencies;
- The prevention of subsequent pneumococcal infection in patients recovering from proven or assumed pneumococcal pneumonia;
- Children at high risk of disease, such as splenectomized children and those with sickle-cell disease.

There is an almost complete lack of information on the burden of pneumococcal disease among adults and the elderly population in developing regions. This illustrates the urgent need for further epidemiological and disease-burden studies on pneumococcal disease. Properly designed phase III trials may provide information both on efficacy and disease burden.

The polysaccharide vaccine has not been used in developing countries where much of the pneumococcal disease burden is found in the under-two age group. Due to poor immune response in children under two years of age, the polysaccharide vaccine is not recommended for routine use in national childhood immunization services. The possibility that the vaccine may provide some protection to newborn infants through systematic immunization of pregnant women is currently being investigated.

(ii) Candidate pneumococcal vaccines

Based on immunological considerations and the results of safety, immunogenicity and efficacy trials, the conjugate vaccines are likely to be more efficient than the polysaccharide vaccine for the prevention of pneumococcal disease in children.

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Poliomyelitis vaccine

Public health strategies

Poliomyelitis is caused by infection with any one of three related enteroviruses: poliovirus types 1, 2 or 3. In 90–95% of infected individuals, poliovirus infection is not apparent, a minor illness is followed by rapid complete recovery with no paralysis. Paralytic poliomyelitis occurs in approximately 0.5% of infections. The virus enters through the mouth and then multiplies in the throat and intestines. The incubation period is 4-35 days and the initial symptoms include fever, fatigue, headaches, vomiting, constipation (or less commonly diarrhoea), stiffness in the neck, and pain in the limbs. Once established in the intestines, poliovirus can enter the blood stream and invade the central nervous system - spreading along nerve fibres. As it multiplies, the virus destroys nerve cells (motor neurons) which activate muscles. These nerve cells cannot be regenerated and the affected muscles no longer function. The muscles of the legs are affected more often than the arm muscles. The limb becomes floppy and lifeless - a condition known as acute flaccid paralysis (AFP). More extensive paralysis, involving the trunk and muscles of the thorax and abdomen, can result in quadriplegia. In the most severe cases (bulbar polio), poliovirus attacks the motor neurons of the brain stem - reducing breathing capacity and causing difficulty in swallowing and speaking. Without respiratory support, bulbar polio can result in death.

In 1988 the World Health Assembly set the goal of worldwide polio eradication. Subsequently, the end of 2005 was made the target date for global certification of the eradication of the disease. Since 1988, WHO has been working with national governments, UNICEF, Rotary International, the Centers for Disease Control and Prevention, and a broad array of public and private partners in order to support the work of eradicating polio from the countries where the disease has been endemic. The four principal strategies of polio eradication are: routine immunization of infants, supplementary immunization through national immunization days (NIDs), surveillance for acute flaccid paralysis (AFP) and mop-up immunization campaigns.

Routine immunization of infants

All infants should receive a minimum of four doses of oral polio vaccine (OPV) during their first year of life. Routine immunization provides a basic level of immunity against polio. High routine immunization coverage also reduces the amount of circulating wild poliovirus, thus facilitating eradication.

Supplementary immunization

A national immunization day is a mass campaign that aims to deliver two doses of OPV to all children aged less than five years in an entire country. In a subnational immunization day (SNID) the same approach is used in a large area of a country. All children are immunized regardless of their prior immunization status. The two rounds are approximately a month apart and are normally conducted during the cool dry season in order to facilitate the logistics and improve the immune response to vaccination. NIDs rapidly increase population immunity, particularly intestinal secretory IgA, to high levels that interrupt the circulation of wild polioviruses.

Acute flaccid paralysis surveillance

AFP surveillance aims to report and investigate all cases of acute flaccid paralysis occurring in children aged under 15 years, including Guillain-Barré syndrome and all cases of suspected polio in persons of any age. Stool specimens from every AFP case are subjected to virological analysis in a WHO-accredited laboratory in order to determine whether wild poliovirus has caused the paralysis.

Mop-up immunization

Mop-up immunization is conducted when poliovirus transmission becomes focal. Surveillance data are used to identify the final reservoirs of transmission in a country. In order to increase coverage to the highest possible level, mop-up activities involve a strategy of house-to-house vaccine delivery. All children aged under five years are immunized with two doses of OPV, regardless of their prior immunization status. This strategy is also employed in the event of an importation or an outbreak.

WHO recommendations for routine immunization

The immunization schedule recommended by WHO calls for the four doses of OPV to be given at birth and at 6, 10 and 14 weeks of age in polio-endemic countries. In countries where the disease is not endemic the birth dose may be omitted, with the fourth dose given at the time the child is brought for vaccination against measles, or at any other contact with the health system in the first year of life. There should be an interval of at least four weeks between doses. OPV is composed of three types of attenuated poliovirus (Sabin strains). The purpose of recommending several doses is to assure seroconversion against all types of poliovirus.

Inactivated polio vaccine (IPV) is not recommended for routine immunization in developing countries because of its high cost, uncertain efficacy if given at 6, 10 and 14 weeks, and the added logistical considerations such as the need for syringes and needles. The Global Technical Consultative Group is evaluating the potential for using IPV in developing countries in the post-certification era. Because of the time needed to complete these deliberations and research, countries should plan to continue using OPV for the foreseeable future.

Special issues

HIV-infected infants and children: In countries where HIV is highly endemic, infants and children should be immunized with OPV according to standard schedules.

Certification: A three-year period of zero indigenous wild poliovirus in all countries, in the presence of high-quality AFP surveillance, is the basis of an independent commission's determination of when a WHO region can be certified as polio-free. In 1994 the Region of the Americas was certified as being polio-free by the Global Commission for the Certification of the Eradication of Poliomyelitis, in 2000 the Western Pacific Region acquired this status, followed by the European Region in 2002. When all regions have been certified to be polio-free the global certification commission will review the global data and, if satisfied, will issue a formal declaration of global certification. In contrast to regional certification, global certification will require the completion of appropriate laboratory containment activities in all countries.

Containment: After polio has been eradicated the only reservoirs of wild polioviruses will be laboratory stocks and OPV and IPV production facilities. The accidental or intentional release of wild poliovirus from a laboratory or manufacturing facility could have major public health implications. With broad international consultation, WHO has prepared a plan for the containment of wild polioviruses in secure laboratory facilities so as to minimize the likelihood that poliovirus can be released from laboratories into communities.

Circulation of vaccine-derived poliovirus: An outbreak of paralytic polio occurred in 2000 in Hispaniola Island, the cause of which was a vaccine-derived virus that reverted and acquired both the neurovirulence and transmissibility characteristics of wild poliovirus. This resulted in the virus being transmitted widely and causing disease. Low routine immunization coverage was a major contributory factor. Transmission has been interrupted through NIDs and the use of OPV. The discovery of similar outbreaks in the Philippines in 2001 and Madagascar in 2002 demonstrate that, although rare, similar outbreaks are possible. In order to prevent such outbreaks, all countries must continue to maintain high polio vaccine coverage and active surveillance.

Administration summary

	OPV	IPV
Type of vaccine	Live oral polio vaccine (OPV)	Inactivated polio vaccine (IPV) given by injection
Number of doses	Four in endemic countries	2–3 depending on country schedule
Schedule	Birth dose,* 6, 10, 14 weeks	2–3 doses in first year of life
Booster	One lifetime dose in countries where the disease is endemic. Most doses given during NIDs are supplemental	One booster commonly given in industrialized countries
Contraindications	None	None
Adverse reactions	VAPP very rarely (approximately one case per 3 million doses administered)	None significant
Special precautions	Children known to have rare congenital immune deficiency syndromes should receive IPV rather than OPV.	None

* In polio-endemic countries.

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Rabies vaccine

Summary and conclusions

Rabies is a viral zoonosis and carnivores such as foxes and raccoons, as well as many bat species, are wildlife hosts of the rabies virus in nature. Globally, in terms of human disease dogs represent the most important reservoir. Infection of humans usually follows bites by rabid animals and is almost invariably fatal once signs of disease occur. More than 2.5 thousand million people live in regions where rabies is endemic. It is estimated that each year at least 50 000 people die from rabies, and more than 10 million receive post-exposure vaccination against this disease. Children aged 5–15 years are at particular risk. More than 99% of all human deaths from rabies occur in Africa, Asia and South America; India alone reports 30 000 deaths annually.

For more than 100 years, rabies vaccines of nerve tissue origin have been used for vaccination of humans following exposure to rabid animals. These vaccines are considered to be inexpensive, but are of relatively low potency per dose, and those produced on sheep or goat brain are frequently associated with serious adverse events. Many of the poor populations most at risk of contracting rabies still depend on nerve tissue vaccines, whereas in affluent populations safe and highly efficacious rabies vaccines produced in cell culture (hereafter referred to as cell-derived rabies vaccines) have been available for 20–30 years. Cell-derived vaccines are used not only for post-exposure treatment, but also for pre-exposure (pre-emptive) protection of persons at risk.

In many countries very potent veterinary rabies vaccines are produced and widely applied for immunization of domestic animals (mostly dogs and cats), and in industrialized countries oral vaccines are used for the immunization of wildlife hosts of rabies virus. So far, however, attempts at controlling animal rabies have largely failed in most poor regions of the world.

Public health impact of rabies

In about 100 countries, rabies is enzootic in both wild and domestic animals and poses a potential threat to a considerable proportion of the more-than 2.5 thousand million people living in these areas. Some island states such as Iceland, Japan and the United Kingdom, and European states such as Belgium, Finland, France, Greece, Norway, Portugal, Spain, Sweden and Switzerland, are now considered free of rabies. Until 1995, Australia was considered to be rabies-free, but in 1996 a rabies-related lyssavirus (type 7) was discovered in flying foxes, a bat species. More than 99% of all human deaths due to rabies occur in tropical developing countries in Africa, Asia and South America.

Among human infections, rabies is believed to be the tenth most common cause of death. Once clinical symptoms have occurred, the disease is almost invariably fatal. However, reporting is often incomplete and the estimated 50 000 deaths per year may be an underestimate. Asia accounts for more than 90% of all rabies fatalities. India alone reports 30 000 deaths per year, i.e. an annual incidence of approximately 3 deaths per 100 000 population. Annual incidences of 0.01–0.2 deaths per 100 000 are reported from Latin America. In Africa, 0.001–13 deaths per 100 000 are reported, but rabies is grossly underreported in many countries.

Although all age groups are susceptible, rabies is most common in people aged under 15 years, with 30%–50% of post-exposure treatments given to children aged 5–14 years, the majority being male. The most severe injuries such as multiple head and/or neck bites have the shortest incubation period and tend to occur in the youngest children. Since many of these exposures are never reported, it is likely that there is a high proportion of young children dying from undiagnosed rabies.

Whereas most wild mammals can become infected, susceptibility to rabies shows considerable variation among species. In southern Africa, parts of the Caribbean, North America and Europe the principal mammalian reservoir are wild carnivores. In Europe and the Arctic and sub-Arctic regions, the main wildlife vector is the fox. In North America striped skunks, racoons, coyotes and insectivorous bats also transmit rabies. In Africa animal reservoirs include the mongoose and jackal, in western Asia the wolf and in Latin America the vampire bat. However, in Asia, parts of Latin America and large parts of Africa, dogs remain the principal host and transmitter of rabies to humans.

In North America and Europe, rabies in domestic animals is well under control. However, in both Canada and the United States, the rapid spread of rabies in racoons is currently causing concern. In Europe, 20 years of oral fox vaccination programmes have reduced the annual number of infected animals from over 20 000 to approximately 6 000, with countries in central and eastern Europe accounting for most cases today.

Post-exposure treatment to prevent human rabies using a combination of vaccine and rabies immunoglobulin, and under certain circumstances elimination of dogs, have significantly contributed to a reduction of human deaths from rabies in countries such as China, Indonesia, Thailand and Viet Nam. However, approximately 6 million people still receive post-exposure treatment annually, the majority being in China and India.

The pathogen and disease

Rabies virus belongs to the genus *Lyssavirus* within the family *Rhabdoviridae.* The genus *Lyssavirus* includes seven types, of which type 1 represents the classic rabies virus.

The rabies virus is bullet-shaped and measures approximately 180 x 75 nm. The RNA genome encodes five proteins: the glycoprotein (G) is the primary structural component of the surface spikes embedded in the viral envelope and is associated with the smaller M protein. Enclosed by the host-cell derived envelope is an infectious viral core of nucleocapsid (N) proteins, thus encapsidating the viral genome and the RNA polymerase. The NS protein is associated with the nucleocapsid.

Rabies virus is stable between pH 3 and pH 11 and may survive for many years at –70°C or when freeze-dried and kept at 0–4°C. It is rapidly inactivated by desiccation, UV and X-ray exposure, sunlight, trypsin, b-propiolactone, ether and detergents.

Rabies is a zoonosis and human infection by rabies virus occurs usually as a result of a transdermal bite or scratch by an infected animal. Transmission may also occur when infectious material, usually saliva, comes into contact with the victim's mucosa or fresh skin lesions, or on very rare occasions through inhalation of virus-containing aerosol. The virus first binds to receptors on the muscle cells, but is highly neurotropic through the rest of the infection. In general the incubation period is inversely related to the size of inoculum, degree of innervation and proximity of the bite to the central nervous system. With extremes of four days to several years, the incubation period is generally between 20 and 90 days.

The initial symptoms of rabies are often mild fever and pain or paresthesia at the wound site. As the virus spreads in the central nervous system, progressive encephalitis develops. Furious rabies is a rapidly fatal brainstem encephalitis characterized by hydrophobia or aerophobia, hyperactivity and fluctuating consciousness. Bizarre behaviour and a lack of focal neurological signs are typical features. Phobic reflexes involve jerky inspiratory spasms that may end in opisthotonos, generalized convulsions and cardiorespiratory arrest. The disease is almost always fatal and without intensive care the patient will die within a few days. Paralytic rabies runs a less dramatic course, but the final outcome is the same. Flaccid paralysis ascending with pain and fasciculation in the affected muscles and mild sensory disturbances will precede death from bulbar and respiratory paralysis. However, even in the absence of intensive care, such patients may survive for about a month.

No tests are currently available to diagnose rabies infection in humans before the onset of clinical disease. Furthermore, since the virus resides intracellularly, probably within myocytes or neurones at the site of the bite, it is immunologically protected, difficult to detect and does not stimulate antibodies until late in the infection. Treatment should therefore be implemented promptly in every case suspected of infection with rabies virus. To prevent a fatal outcome, therapy must be initiated before the virus reaches the central nervous system and clinical signs appear.

Protective immune response

In natural infection, rabies virus is largely unavailable to the immune system and the immune response is usually slow. Thus, there is a delayed antibody response to both the G and N protein and the number of natural killer cells are in general reduced, implying deficits of immune recognition or activation. Furthermore, in patients with paralytic rabies, lymphocyte proliferation seems to be impaired.

Following vaccination with modern cell-derived rabies vaccines, a prompt and highly protective antibody response is elicited. Immunity is believed to depend mainly upon the CD4+ T-cell dependent neutralizing antibody response to the G protein. Also, cell-mediated immunity has long been recognized as an important part of the defence against rabies. Cells presenting fragments of the G protein are the targets of cytotoxic T-cells and the N protein induces T-helper cells.

The justification for rabies vaccination

In the majority of industrialized countries, human rabies is under control, mainly due to oral vaccination of wildlife and mandatory parenteral vaccination of domestic animals. However, about 98% of human rabies occurs in regions with large numbers of both stray and domestic dogs. Measures to control rabies in these areas, such as bait-based vaccination of wildlife, elimination of stray dogs and vaccination of domestic dogs, have not yet been fully implemented.

Rabies is currently an incurable disease. Antiviral agents, interferon and massive doses of rabies immune globulin have been used to treat human cases, but seem only to prolong the clinical course without affecting fatality. However, post-exposure treatment initiated at an early stage using rabies vaccine in combination with rabies immune globulin may be 100% effective in preventing death. Given pre-emptively, modern rabies vaccines produce an antibody response in over 99% of vaccinees. In the United States, more than 50 000 doses have been given to persons at increased risk of rabies, and not a single case has been reported among these recipients.

Rabies vaccines

More than 100 years ago, Louis Pasteur and his colleagues developed the first crude rabies vaccine based on attenuated virus from desiccated nerve tissue. Unfortunately, the majority of post-exposure immunizations against rabies are still performed with vaccines of crude nerve tissue origin. Although continuously improved over the years, inactivated vaccines produced in sheep or goat brains (Semple) or suckling mouse brain (Fuenzalida) may be associated with serious adverse events. Possible post-vaccinal neurological reactions may include meningoencephalitis, meningoencephalomyelitis, mononeuritis multiplex, dorsolumbar transverse myelitis and ascending paralysis of the Landry type, usually occurring between one and two weeks after the first injection. With the Semple-type vaccines, the incidence of neurological reactions varies between 1 in 200 and 1 in 1600 recipients, with a lethality of up to 14%. Vaccines of the Fuenzalida type are ssociated with neurological complications in about 1 in 8000 to 1 in 27 000 courses.

Furthermore, in terms of protective potency these vaccines are inferior to modern cell-derived vaccines. A complete post-exposure treatment using nerve tissue vaccines involves a prolonged and painful immunization course of up to 23 injections. Obviously, these vaccines are not recommended for pre-exposure immunization.

The human diploid cell rabies vaccine was introduced in 1967 and is regarded as the gold standard for rabies vaccines. However, the more recently developed and less expensive purified chick embryo cell vaccine and purified Vero cell rabies vaccine have comparable characteristics. They are all lyophilized and must be reconstituted. The potency of all cell-derived vaccines is assessed using a National Institutes of Health test and the WHO requirement is a potency of at least 2.5 IU per intramuscular dose.

Human diploid cell rabies vaccines are based on the Pitman-Moore L503 strain or, in one case, the Flury strain of rabies virus. Human diploid cell rabies vaccines have been given to more than 1.5 million people worldwide. Its protective efficacy in situations of heavy exposure has been shown in the Islamic Republic of Iran where none of 45 persons who received post-exposure treatment with this vaccine developed rabies following severe bites by rabid dogs or wolves.

The purified Vero cell rabies vaccine contains the Wistar strain of the virus, but with the Vero cell line as substrate. Clinical studies with the purified Vero cell vaccine show neutralizing antibody responses both after primary and secondary immunizations that are fully comparable to those seen after vaccination with the human diploid cell vaccines. In Thailand, post-exposure treatment using purified Vero cell vaccine and rabies immune globulin has been shown to be protective.

Purified chick embryo cell rabies vaccine is prepared from inactivated rabies virus of the Flury LEP-25 strain. No clinically important differences were observed when this vaccine was evaluated together with human diploid cell vaccines in studies on post-exposure protection of animals and humans and in pre-exposure immunogenicity studies. More than 30 million doses of the purified chick embryo cell vaccine have been administered worldwide.

Purified duck embryo rabies vaccine showed similar qualities to the other cell-derived rabies vaccines, but is no longer manufactured.

Despite applying potent, modern, cell-derived vaccines, about one “failure” in 1 million post-exposure treatments does occur. Careful analyses show that such failures are almost always associated with severe lesions on or near the head and/or inappropriate administration of the treatment.

There are no contraindications to any of these vaccines being used for post-exposure treatment. Should an allergic reaction occur, the modern vaccines of different cell substrate origin may replace each other. Pregnancy is not a contraindication to post-exposure treatment.

Although associated with mild and transient reactions, all the cell-derived rabies vaccines are considered safe. With human diploid cell vaccines, which are most thoroughly investigated, pain, erythema and swelling or itching at the injection site occur among 30%–74% of the recipients. Systemic reactions involving headache, nausea, abdominal pain, muscle aches or dizziness are reported among 5%–40% of vaccinees, and allergic oedema in 0.1%. One study reports fever among 3.6% of recipients of the human diploid cell vaccine. Systemic allergic reactions characterized by generalized urticaria accompanied in some cases by arthralgia, angiooedema, fever, nausea and vomiting have been reported. They are uncommon in persons receiving primary vaccination, but have occurred in up to 6% of persons receiving a booster dose, with onset after 2–21 days. These reactions have been shown to follow the development of IgE antibodies to b-propiolactone altered human serum albumin in the vaccine (b-propiolactone is used as an inactivating agent). According to the manufacturers of purified Vero cell rabies vaccine and purified chick embryo cell vaccine, allergic reactions are very rare after both primary and booster doses with these vaccines. Studies on the purified Vero cell rabies vaccine report local and general reactions in 10.6% of post-exposure treatment patients and complaints of mild to moderate reactions in 7%. Also, among intradermal or intramuscular recipients of this vaccine, low-grade fever was the only significant systemic event, occurring in 8% of all subjects and most frequently following intramuscular vaccination. In the same study, pruritus at the injection site was the only significant local reaction. Among 88 healthy adults receiving a total of 292 doses of purified chick embryo cell vaccine, 16.4% reported local side-effects, whereas 15.1% reported general symptoms.

Other cell-derived vaccines are available on a national scale only. For example, in the United States the Kissling rabies strain has been adapted to replication in lung fibroblasts of fetal rhesus monkeys. The resulting vaccine, which is given according to the same pre- and post-exposure schedules as the human diploid cell vaccine, is considered equally effective and may less often cause allergic reactions. In Japan, a vaccine type similar to the purified chick embryo cell vaccine, but based on the Flury HEP strain, has reached limited distribution. A primary hamster kidney-cell rabies vaccine is mainly used in China where it was licensed in 1989. Each year more than 5 million doses of this vaccine are administered in China, where it has now completely replaced the Semple-type rabies vaccine. A chromatographically purified version of the purified Vero cell rabies vaccine is about to be licensed in Europe.

Current strategies for rabies vaccination

Human deaths from rabies can effectively be prevented by vaccination, either pre-exposure vaccination or as part of post-exposure treatment.

Pre-exposure vaccination may be performed with any of the modern cell-derived vaccines and is recommended for anyone at increased risk of exposure to rabies virus. Traditionally, this recommendation includes laboratory staff, veterinarians, animal handlers, wildlife officers with frequent exposure to potentially infected animals as well as visitors to highly rabies-enzootic areas who may be exposed to rabies hosts. However, according to age-stratified studies of incidence, those at greatest risk are probably children living in rabies-enzootic regions of the developing world.

The pre-exposure schedule requires intramuscular doses of 1 ml or 0.5 ml, depending on the vaccine type, given on days 0, 7 and 28. Major vaccine manufacturers recommend one booster dose after one year, and to ensure protection in persons at continued risk, booster vaccinations every five years, or ideally, at intervals dictated by regular testing for antirabies antibodies (titres >0.5 IU/ml required for protection). On the other hand, studies with the human diploid cell vaccine and the purified Vero cell rabies vaccine have shown that 10 years after a pre-exposure series followed by a single booster dose after one year, more than 96% of the vaccinees still have neutralizing antibodies against rabies virus.

The indication for post-exposure vaccination with or without rabies immune globulin depends on the type of contact with the rabid animal. Types of contact are: category I – touching or feeding animals, licks on the skin; category II – nibbling of uncovered skin, minor scratches or abrasions without bleeding, licks on broken skin; category III – single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks. For category I no treatment is required, whereas for category II immediate vaccination and for category III immediate vaccination and administration of rabies immune globulin are recommended in addition to immediate washing and flushing of all bite wounds and scratches. Depending on vaccine type, the post-exposure schedule prescribes intramuscular doses of 1 ml or 0.5 ml given as four to five doses over four weeks. For rabies-exposed patients who have previously undergone complete pre-exposure vaccination or post-exposure treatment with cell-derived rabies vaccines, two intramuscular doses of a cell-derived vaccine separated by three days are sufficient. Rabies immune globulin treatment is not necessary in such cases. The same rules apply to persons vaccinated against rabies who have demonstrated neutralizing antibody titres of at least 0.5 IU/ml.

In order to reduce the cost of post-exposure treatment, intradermal multi-site regimens using a fraction of the intramuscular volume per intradermal inoculation site have been developed. Purified Vero cell vaccine has been given intradermally to more than 70 000 recipients in Thailand, where it has been in routine use for several years. Intradermal rabies vaccination is also recommended by the ministries of health of Sri Lanka (since 1995) and the Philippines (since 1997). In each of these countries the introduction of this route for post-exposure treatment has permitted the discontinuation of the local production of vaccines prepared on brain tissue. Only the cell-derived vaccines that meet the WHO requirements regarding safety, potency and efficacy for this application may be considered for intradermal use. Although rabies vaccines are usually administered under qualified medical supervision, field experience from routine infant immunization services with other intradermally injected vaccines highlights the potential difficulties in assuring proper delivery. This emphasizes the need for appropriate staff training to ensure correct storage, reconstitution and injection. Provided that a correct sterile technique is used, the remaining doses may be kept in the vial at 2 – 8°C and used for another patient within six hours after reconstitution.

WHO position on rabies vaccines

All the above internationally available cell-derived rabies vaccines are of assured quality. If used properly, when necessary in combination with rabies immune globulin and immediate wound treatment, they are regarded as 100% effective in preventing death from rabies.

Despite development of less expensive vaccines against rabies and less vaccine-consuming administration schedules, many of the countries particularly affected by this disease can afford only the less efficacious and relatively dangerous nerve tissue vaccines. Due to their high rates of adverse effects, it is imperative that these vaccines be replaced by the more potent and safe cell-derived products. Veterinary rabies vaccines should not be used for humans.

Pre-exposure immunization is recommended for all individuals living in or travelling to highly rabies-enzootic areas, or who are exposed to rabies by nature of their occupation. Surveillance data should identify the regions where rabies is a major problem. On the basis of careful assessment of the public health impact and of cost-benefit analyses, decisions should be made whether or not to start pre-exposure vaccination of the population segments at highest risk, such as children aged 5–15 years. Studies from Viet Nam have demonstrated the feasibility, safety and immunogenicity of giving two doses of Vero cell vaccine intramuscularly at two and four months of age, or three intradermal doses at two, three and four months of age. WHO encourages carefully designed studies on the feasibility and impact of incorporating modern rabies vaccines in the early immunization services of infants and children in communities where rabies is a major problem. In this context, the long-term outcome of intradermal pre-exposure vaccination of young children needs further clarification.

Efforts to eliminate rabies must involve vaccination of the animal host, mainly dogs. This implies control of the dog population, vaccination of stray dogs using baits as well as traditional vaccination of owned dogs. It has been shown that rabies vaccination of 80% in dogs is sufficient to break the canine transmission chain.

Post-exposure treatment is recommended for all category II and III exposures to rabies virus. Factors that should be taken into consideration when deciding whether or not to initiate such treatment are the category of exposure, the presence of rabies in the area where the contact occurred or from which the animal came, and the animal species involved. Also, the vaccination status and clinical features of the animal involved, the type of vaccine used and the availability of the animal for observation must be considered, as should be, if available, the results of laboratory testing of the animal.

If post-exposure treatment must be given to immunocompromised individuals, HIV-positive persons, people under malaria chemoprophylaxis or people under anaesthesia, intramuscular vaccine and rabies immune globulin are mandatory and their antibody responses should be monitored serologically. It should be noted that in individuals aged over 50 years the serological response to rabies vaccination may be less efficient than in younger people. However, all seem to seroconvert after five doses.

Although the costs of the modern cell-derived vaccines have been decreasing since their introduction on the market, and cost-reducing regimens have been developed, these vaccines remain prohibitively expensive for the most vulnerable communities in developing countries. WHO therefore endorses initiatives to facilitate the use of modern and potent rabies vaccines and encourages increased accessibility of high-quality rabies immune globulin.

Where rabies poses a significant health problem, and money and vaccines are in short supply, the use of the intradermal route for post-exposure treatment should be considered. Also, it is important to assess the efficacy of multi-site intradermal application in the absence of rabies immune globulin.

This chapter was last published as a WHO position paper: Rabies vaccines. WHO position paper. *Weekly Epidemiological Record,* 2002, 77, 109–120, and is available on the Internet at http://www.who.int/wer/pdf/2002/wer7714.pdf.

Administration summary for pre-exposure rabies

Type of vaccine	Inactivated (from cell culture or embryonated egg vaccine)
Number of doses	Three
Schedule	Intervals of 7 and 1–28 days given by the intramuscular or intradermal route
Booster	After 1 year then every 5 years
Contraindications	Severe reaction to previous dose
Adverse reactions	Mild local or systemic reactions; rare neuroparalytic reaction reported
Special precautions	Do not use animal-brain-derived vaccines

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Rotavirus vaccine

Summary and conclusions

The rhesus reassortant rotavirus vaccine is currently still licensed by the FDA under the name RotaShield. However, the vaccine was withdrawn from the market by the manufacturer after the vaccine was associated with several cases of intussusception in the United States.

Rotavirus is the most common cause of severe diarrhoeal disease in infants and young children all over the world, and is an important public health problem, particularly in developing countries. The only control measure likely to have a significant impact on the incidence of severe disease is vaccination. Natural infection protects children against subsequent severe disease. Globally, four serotypes are responsible for the majority of rotaviral disease, but additional serotypes are prevalent in some countries. At least seven vaccine candidates are under development, but currently only the tetravalent rhesus rotavirus vaccine (RRV-TV) is licensed in the United States. In developed countries, and in Venezuela, this vaccine prevents severe rotaviral diarrhoea in children under two years of age. However, as rotavirus vaccine candidates appear to be less effective in developing countries than in developed, additional studies of this vaccine are warranted, particularly in Africa and Asia, to ensure that the vaccine will work as expected in the global context.

Given the worldwide importance of rotavirus disease, and the proven efficacy of the RRV-TV vaccine, at least in industrialized countries, WHO encourages the use of a safe and effective rotavirus vaccine in industrialized countries as a valuable first step towards global control of this disease.

The incidence of severe and fatal rotavirus diarrhoea is particularly high in developing countries. While the vaccine worked well in Venezuela and may work well in other developing countries, it would be premature to include this vaccine in the national childhood immunization services in developing countries until studies in Africa and Asia are available to confirm its efficacy in a full range of settings.

Public health impact

Rotavirus infection has a worldwide distribution, and is the most common cause of severe diarrhoea in young children. Almost all children are infected by the age of three to five years. More than 125 million cases of diarrhoea each year are attributed to rotavirus. It is estimated that rotavirus causes 25% of all deaths due to diarrhoeal disease, and 6% of all deaths in children under five years of age. The disease follows an incubation period of one to two days, and is characterized by acute onset of vomiting, fever and profuse watery diarrhoea. Although the infection is usually mild, severe disease may rapidly result in life-threatening dehydration if not appropriately treated. The greatest disease burden is in developing countries, where 20%–40% of annual hospitalizations for childhood diarrhoea, and about 600 000 deaths each year, are associated with this infection. In developing countries most cases of severe rotavirus disease occur in infants whereas in the industrialized world the majority of severe cases occur beyond the first year of life. In Australia, England and Wales, Japan and the United States, rotavirus infection is shown to be responsible for 34%–52% of hospitalizations for childhood gastroenteritis, but mortality from rotavirus diarrhoea is extremely rare in those countries.

In tropical developing countries, rotavirus disease occurs throughout the year. Several viral serotypes may operate simultaneously in the same geographical area, and infection with more than one strain in individual patients is common. In industrialized countries in temperate climates, rotavirus infections peak during the winter season and mixed infections are uncommon. Rotavirus is transmitted by the faecal-oral route and a small inoculum may cause infection. Animal reservoirs for human rotavirus infection are not known to exist, and asymptomatic human carriers do not seem be a major source of sporadic cases. Rotavirus may cause hospital infections in children, and are associated with diarrhoea in travellers, the elderly and carers of small children.

The pathogen

Rotaviruses belong to the *Reoviridae* family and are 70 nm, non-enveloped viruses with 11 segments of double-stranded RNA. Groups are specified by inner capsid antigen, and only group A is an important cause of disease in children. The two structural proteins of the outer capsid, the VP7 glycoprotein (or G protein) and the VP4 protease-cleaved protein (or P protein) define the serotypes of the virus against which neutralizing antibodies are derived. Worldwide, G1-G4 are the serotypes most commonly linked to rotavirus diarrhoea, although additional serotypes appear to play a role in some settings. Cross-reactivity between human and several animal rotavirus antigens has been recorded and occasionally, rotavirus strains isolated from humans are shown to be reassortants between human and animal strains. However, it is unlikely that this phenomenon has had a significant impact on the natural history of rotavirus infection or disease, and humans appear to be the only reservoir of human strains. Rotavirus is not inhibited by existing antiviral drugs. Simple and inexpensive immunoassays are available for detection of rotavirus in the stool.

Protective immune response

The immune correlates of protection to rotavirus infection are not well defined. Neutralizing antibodies to the two outer capsid antigens VP7 and VP4, and IgG or IgA antibodies to the inner capsid antigen, VP6, have each been correlated with protective immunity by some investigators. A rotavirus-specific IgA response to VP6 is believed to be essential for protective immunity in the intestinal mucosa. It is likely that cell-mediated immunity is related to clearing infection. Immunogenicity of rotavirus vaccines is usually measured by serum IgA seroconversion or by level of neutralizing antibodies to the vaccine strain.

A child's first rotavirus infection results in a serotype-specific immune response, which is broadened upon subsequent exposures. Immunity acquired during these first infections protects against severe disease on subsequent exposures to rotavirus of different serotypes. Breastfeeding may provide some protection against the disease in the very young infant. Symptomatic rotavirus infection occurs primarily in the first two to three years of life, during which time most children worldwide develop immunity to rotavirus diarrhoea.

The justification for vaccine control

Rotavirus diarrhoea represents an important global public health problem, and the development of a vaccine has been given high priority by WHO. As the incidence of rotavirus diarrhoea does not differ dramatically between developing and developed countries, it is unlikely that environmental improvements will have a great impact on the disease incidence, although mortality due to rotavirus decreases with improvement in standard of living. Oral rehydration is the treatment of choice and can be life-saving, but does not reduce dissemination of the virus. Specific antirotavirus chemotherapy is currently not available. Natural immunity has been demonstrated by the immunity conferred by one or several natural infections, and a decade of experience with different candidate vaccines clearly supports the concept of immune prophylaxis through vaccination. In industrialized countries, experimental oral rotavirus vaccines have shown a protective efficacy of 80% or more against severe disease. Except for mild to moderate fever in about 20% of the vaccinees on day four, there have been minimal adverse reactions following vaccination, and cost-effectiveness studies indicate that, depending upon the price, a rotavirus vaccine could be cost-effective.

Rotavirus vaccine candidates

The first rotavirus vaccines were based on rotavirus strains of either bovine or simian origin attenuated by passaging in laboratory cell cultures. As clinical trials with these single strain (monovalent) vaccine candidates showed varying results, polyvalent vaccines were developed. In these vaccines selected genes from common serotypes of human rotaviruses have been reassorted into suitable animal strains. Currently, several such reassortant rotavirus vaccines are being developed, of which one is a tetravalent rhesus-human rotavirus combination, others are tetravalent/pentavalent combinations of human-bovine strains. One recent vaccine candidate is based entirely on a human strain of rotavirus.

The only rotavirus vaccine currently licensed is a reassortant vaccine based on a rhesus rotavirus (RRV) strain that has a VP7 protein which is closely related to the human rotavirus serotype G3 protein. To induce protective immunity against the remaining most common serotypes, single gene substitution reassortant vaccines incorporating human rotavirus G1, G2 or G4 specificity were developed, tested individually for safety and immunogenicity, and subsequently combined into the tetravalent G1-G4 vaccine cocktail (RRV-TV). An oral dose of this vaccine (viral concentration 4 x 100 000 pfu/dose) is administered three times at intervals of about four weeks to infants aged between 6 and 26 weeks.

The safety, immunogenicity and efficacy of this vaccine have been studied in a large number of infants in Finland, Venezuela and the United States. Field trials in the same countries showed an efficacy of 49%–68% against any rotavirus diarrhoea, and 64%–100% efficacy against severe disease. Also, the duration of the diarrhoea was significantly reduced by this vaccine. Although serotype G1 was the predominant cause of rotavirus disease during all these trials, the RRV-TV was found to protect against the occasional non-serotype G1 disease as well. The result of the recently conducted trial in Venezuela is particularly encouraging because it demonstrated the efficacy of the vaccine in a poor socioeconomic setting. A 10-fold lower dose of the vaccine showed little or no protective effect in trials performed in Brazil and Peru, suggesting that the efficacy may be dose-related, but the low rates of severe disease in these studies complicates interpretation of these results.

Although the vaccine strain is found in the stools of vaccinated children, there is no evidence of vaccine-induced disease or of seroconversion among their contacts. Breastfeeding does not interfere significantly with the efficacy of the RRV-TV vaccine, and RRV-TV vaccination does not impair the immunity induced by concurrent childhood vaccines such as DTP, oral polio, hepatitis B and Hib vaccines.

Adverse effects

During the third or fourth days following the first dose of the RRV-TV vaccine, fever of 38–39°C, accompanied by irritability and decreased appetite, may occur in up to 20% of the vaccinees. Neither vomiting nor diarrhoea has been recorded in this group.

Contraindications

As with most other live vaccines, rotavirus vaccines should not be given to children with known or suspected immunodeficiency such as congenital immune disorders, HIV-infection and malignancies, or who are undergoing immunosuppressive therapy.

WHO position on rotavirus vaccines

The WHO steering committee on diarrhoeal disease vaccines maintains rotavirus vaccine development as its first priority. Although WHO encourages worldwide introduction of rotavirus vaccines, emphasis is on countries with the highest disease burden. However, because of differences in epidemiology, health priorities and economic capacity, rotavirus vaccines will be introduced at different rates into national immunization services.

The background information presented above shows that rotavirus disease is a considerable medical and socioeconomic problem worldwide. Only one rotavirus vaccine candidate, namely the RRV-TV vaccine, is currently licensed. Ample evidence shows that this vaccine provides efficient protection against severe rotavirus disease in children under two years of age in industrialized countries. Similar encouraging results have been obtained in a single trial in Venezuela. The RRV-TV vaccine is safe, and easily adapted to national childhood immunization services. Oral administration is important from the logistic point of view. So far, no lasting substantial interference with simultaneously administered vaccines has been reported. The introduction into industrialized countries of safe and efficacious rotavirus vaccines should be welcomed as an important first step towards global control.

Before rotavirus vaccines may be recommended for large-scale immunization in developing countries, it is essential that protective efficacy be documented in developing country settings. Hence, efficacy studies are strongly encouraged, particularly in Africa and Asia.

If affordable prices for the vaccines can be achieved, rotavirus immunization is likely to be given high priority in all areas where rotavirus infection is recognized as a public health problem.

This chapter was last published as a WHO position paper: Rotavirus vaccines: WHO position paper. *Weekly Epidemiological Record,* 1999, 74:33–40, and is also available on the Internet at http://www.who.int/wer/pdf/1999/wer7405.pdf. It will be updated as new information becomes available.

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Rubella vaccine

Summary and conclusions

Rubella occurs worldwide and is normally a mild childhood disease. However, infection during early pregnancy may cause fetal death or congenital rubella syndrome (CRS); the latter characterized by multiple defects, particularly to the brain, heart, eyes and ears. CRS is an important cause of hearing and visual impairment and mental retardation in countries where acquired rubella infection has not been controlled or eliminated.

Although the burden of CRS is not well characterized in all countries, it is estimated that more than 100 000 cases occur each year in developing countries alone. Caring for CRS cases is costly because of the permanent disabilities caused by this condition. Cost-benefit studies in developed as well as developing countries have demonstrated that, when combined with measles vaccine in countries with coverage of over 80%, the benefits of rubella vaccination outweigh the costs.

The primary purpose of rubella vaccination is to prevent the occurrence of congenital rubella infection including CRS. Two approaches are recommended: (a) prevention of CRS only, through immunization of adolescent girls and/or women of childbearing age; or (b) elimination of rubella as well as CRS through universal vaccination of infants and young children (with/without mass campaigns), surveillance, and assuring immunity in women of childbearing age.

The currently licensed rubella vaccines in wide international use are based on the live attenuated RA 27/3 strain of the virus. Other attenuated vaccine strains are available in China and Japan. The 27/3 vaccines are propagated in human diploid cells and have proven to be safe and efficacious. Rubella vaccines are commercially available in a monovalent form, a bivalent combination with measles vaccine or mumps vaccine, or as trivalent measles–mumps–rubella vaccine (MMR). Following well-designed and implemented programmes, rubella and CRS have almost disappeared from many countries.

Public health impact

Rubella has a worldwide distribution. It usually occurs in a seasonal pattern (i.e. in temperate zones during the late winter and spring), with epidemics every five to nine years. However, the extent and periodicity of rubella epidemics is highly variable in both developed and developing countries. The reasons for this are not known. Before the introduction of large-scale rubella vaccination, the average age at which children were infected varied between 6–12 years of age in industrialized

areas and 2–8 years of age in urban areas of developing countries. The extent of susceptibility in women of childbearing age varies considerably, with study data ranging from less than 5% in Kuwait to 60% in rural Panama, mainly reflecting epidemiological and socioeconomic differences between the study populations. The highest risk of CRS is found in countries with high susceptibility rates among women of childbearing age. Although low susceptibility rates have been reported in studies of selected populations within some countries, these may reflect local variations, and extrapolating from such studies could mask a significant national benefit from the introduction of rubella vaccination.

Reliable statistics on CRS are rare in developing countries, but the incidence rate of CRS in developed and developing countries before the introduction of rubella vaccine appeared to vary during periods of disease endemicity from 0.1–0.2 per 1000 live births. Epidemic rates varied from 1–4 per 1000 live births without marked differences between industrialized and developing countries. Large epidemics can lead to very high levels of morbidity. The United States epidemic in 1964–1965 resulted in an estimated 12.5 million cases of rubella, over 2000 cases of encephalitis, in excess of 11 250 abortions, over 20 000 cases of CRS, over 11 000 cases of deafness, 3580 blind children and 1800 children with mental retardation.

When immunization is targeted at adolescent girls or women of childbearing age, the epidemiology of rubella is largely unaffected since most infections occur before the age of immunization. With such an approach, the incidence of CRS declines linearly with the level of coverage. However, elimination of CRS cannot be achieved with this strategy, in part because it would require every susceptible woman to be effectively immunized.

Childhood immunization of both sexes reduces the number of infections and extends the inter-epidemic interval by reducing the circulation of rubella virus in the community. Hence, one consequence of a childhood-only immunization service may be an increase in the proportion of susceptibles in the adult population. The higher the vaccination coverage, the more apparent this effect will be. This shift in the proportion of susceptibles in older age groups can result in more cases of CRS than in the pre-vaccination period.

Rubella vaccines for childhood immunization are used in the private sector in a high proportion of countries, including regions where vaccination against rubella is not a formal part of the immunization services. Such private-sector provision can affect transmission dynamics and increase susceptibility in women of childbearing age, as recently demonstrated in Greece.

In many developed and some developing countries, large-scale rubella vaccination during the past decade has drastically reduced or practically eliminated rubella and CRS.

In addition to the requirements for surveillance of any vaccine-preventable disease, there are additional needs specific to rubella because of its impact in pregnancy. Appropriate methods for CRS surveillance include hospital record review, deaf/blind surveys, clinician reporting, and active searches for CRS cases after outbreaks of acquired rubella. Where therapeutic abortions are available, the numbers undertaken because of rubella infection may be a sensitive indicator of the impact of

a rubella immunization service. If resources permit, longitudinal serological surveillance monitors the impact of the immunization service, especially through collection of samples among women attending antenatal clinics. Monitoring changes in age- and sex-specific seroprevalence provides data for identification of necessary modifications to the immunization strategy. Integrating rubella laboratory investigation with activities to strengthen measles and dengue surveillance will allow the detection of circulation of rubella, and confirm clinically suspected cases.

The pathogen and the disease

The rubella virus, a *togavirus* of the genus *rubivirus,* is an enveloped single-stranded RNA virus with a single serotype that does not cross-react with other *togaviruses*. Humans are the only known host. Rubella virus is transmitted by the respiratory route, replicating in the nasopharyngeal mucosa and local lymph nodes. The incubation period ranges from 12 to 23 days, with an average of 18 days. Viraemia occurs five to seven days after exposure and leads to viral spread to different organs. In pregnant women the virus infects the placenta and the developing fetus.

Rubella virus can be found in nasopharyngeal samples from one week before rash onset to two weeks afterwards, with maximal shedding after one to five days. Infants with congenital rubella may excrete the virus for one year or more in pharyngeal secretions and urine. The diagnosis of rubella requires laboratory confirmation, particularly under non-epidemic conditions. Serology is the preferred method for routine laboratory diagnosis. Presence of rubella IgM or demonstration of a significant rise in rubella IgG from paired acute and convalescent sera provide evidence of ongoing or recent rubella infection. Viral isolation is labour-intensive and costly and is not routinely used for diagnosis.

Acquired rubella is characterized by a transient, erythematous rash, conjunctivitis, coryza, postauricular and suboccipital lymphadenopathy, low fever and nausea. Arthralgia and arthritis rarely occur in children, but may affect up to 70% of adults, particularly women. Haemorrhagic manifestations, Guillain-Barré syndrome and encephalitis are rarely reported. Serological studies have shown that 20%–50% of all rubella infections are subclinical.

Congenital rubella infection and CRS are caused by infection in early pregnancy. From just before conception and during the first 8–10 weeks of gestation, rubella infection may result in multiple fetal defects in up to 90% of cases, and often results in miscarriage or stillbirth. The risk subsequently declines. Fetal defects are rarely associated with maternal rubella after the sixteenth week of pregnancy, although sensorineural hearing deficit may occasionally occur up to week 20. The defects associated with CRS are: ophthalmic (e.g. cataracts, microphthalmia, glaucoma, pigmentary retinopathy, chorioretinitis); auditory (e.g. sensorineural deafness); cardiac (e.g. patent ductus arteriosus, peripheral pulmonary artery stenosis, or ventricular septal defects); and craniofacial (e.g. microcephaly). CRS can present with neonatal manifestations that include meningoencephalitis, hepatosplenomegaly, hepatitis, thrombocytopenia and radiolucencies in the long bones (a characteristic and pathognomonic radiologic pattern of CRS). Complications of the thrombocytopenia can be fatal. Interstitial pneumonitis is a complication of CRS in infancy. Infants with CRS who survive the neonatal period may face serious

developmental disabilities (e.g. visual and hearing impairment) and have an increased risk for developmental delay, including autism, type I diabetes mellitus and thyroiditis. A progressive encephalopathy resembling subacute sclerosing panencephalitis (SSPE) has been observed in persons with CRS.

Immune responses to infection

Natural rubella infection normally confers lifelong immunity. There have been rare cases of serologically documented re-infections either after earlier natural infection or after vaccination. Re-infection in pregnancy resulting in CRS has occasionally been reported in women with natural or vaccine-induced immunity, but the risk to the fetus is low. Antibodies are first detectable about 14–18 days after acquired rubella infection, at about the time the maculopapular rash appears. A rise in IgM and IgG levels is observed, but IgM antibody levels wane fairly quickly, and by eight weeks are usually undetectable, while IgG persists. A rubella-specific cell-mediated lymphocyte response begins one week after the humoral response and appears to persist for a lifetime. Passively-acquired maternal antibodies provide protection against rubella for the first few months of life and can affect immune response to the rubella vaccine.

Rubella vaccines

There are a number of rubella vaccines available, either as single antigen vaccines or combined with either measles vaccine (MR), mumps vaccine or measles and mumps vaccine (MMR). Most of the currently-licensed vaccines are based on the live, attenuated RA 27/3 strain of rubella virus, propagated in human diploid cells. The RA27/3 vaccine is highly stable at –70°C. When stored at 4°C, its potency is maintained for at least five years. The vaccine should be stored at 2–8°C and protected from light. Each dose of this vaccine, which is given by the subcutaneous route, contains a defined number of active virus particles (>1000 TCID 50). Other attenuated rubella vaccine strains, such as the Matsuba, DCRB 19, Takahashi, Matsuura and TO-336 strains are used primarily in Japan; the BRD-2 strain is used in China.

The RA27/3 vaccine is highly efficacious. In clinical trials 95%–100% of susceptible persons aged 12 months and older developed rubella antibodies by 21–28 days after vaccination. Vaccination even at nine months of age results in seroconversion rates of more than 95%. Vaccine-induced immunity is generally assumed to be lifelong, although rubella antibodies may fall below detectable levels. A study of persistence of immunity following vaccination with MMR showed that about 97% of vaccinees remained seropositive up to 15 years post-vaccination.

Rubella vaccine is usually administered at age 12–15 months, but can also be administered to children as young as nine months of age. In most countries, the vaccine is given as MR or MMR, and the age of administration is chosen based on the appropriate age for measles vaccination. It may also be administered to older children, adolescents, students, childcare personnel, health care workers, military personnel and adult men in contact with women of childbearing age. Rubella vaccination should be avoided in pregnancy because of the theoretical (but never demonstrated) teratogenic risk. No cases of CRS have been reported in more than 1000 susceptible pregnant women who inadvertently received a rubella

vaccine in early pregnancy. Consequently, there is no need to screen women for pregnancy before rubella vaccination. If pregnancy is being planned, then an interval of one month should be observed after rubella immunization. Rubella vaccination during pregnancy is not an indication for abortion.

Persons with a history of anaphylactic reaction to neomycin or an anaphylactic reaction after a previous dose of rubella vaccine should not receive the vaccination. Rubella vaccines should not be given to persons suffering from advanced immunodeficiency including congenital immune disorders, malignancies and immunosuppressive therapy. However, asymptomatic HIV-positive persons can be immunized. Children with malignant disease or who have had a bone marrow transplant should be immunized against rubella six months after immunosuppressant treatment is stopped. Vaccination should be postponed if the potential vaccinee has a serious illness. Persons with active tuberculosis should not be vaccinated until treatment has been established. Rubella antibodies present in blood products may interfere with rubella vaccination. Therefore, persons who received blood products should wait at least three months before vaccination and if possible, blood products should be avoided for up to two weeks post-vaccination.

Generally, the adverse events following vaccination with the RA27/3 rubella vaccine are mild, particularly in children. Most of the available data on adverse events are for the MMR combination. Common adverse events include pain, redness and induration at the site of injection. Low-grade fever and rash, lymphadenopathy, myalgia and paraesthesiae are commonly reported. Joint symptoms tend to be rare in children (0%–3%) and in men, but are common among vaccinated adolescent and adult females; they include arthralgias (25%) and arthritis (10%) that usually last from a few days to two weeks. These transient reactions seem to occur in non-immune individuals only, for whom the vaccine is important. Thus, fear of unjustified side-effects should not prevent vaccination of women with uncertain rubella immune status. As there is no harm in vaccinating already immune individuals, serological testing before immunization is not necessary. Although concerns have been raised that rubella vaccination of adult women might occasionally lead to chronic arthritis, large epidemiological studies have not supported a role for rubella vaccine in chronic joint disease. Thrombocytopenia is rare and has been reported in less than 1 case per 30 000 doses administered. Anaphylactic reactions are rare after RA27/3 vaccines.

Justification for rubella vaccination services

The primary purpose of rubella vaccination is to prevent the occurrence of congenital rubella infection including CRS, which is an important cause of deafness, blindness and mental retardation. The burden of CRS is not well characterized in all regions of the world. However, more than 100 000 cases of CRS may occur each year in developing countries alone.

Rubella vaccination is included in national immunization services in the majority of countries and territories of the world. The vaccines are highly protective and without significant adverse effects. Caring for CRS cases is costly in all countries. All cost-benefit studies of rubella vaccination, in developing and developed countries, have demonstrated that the benefits outweigh the costs and that rubella vaccination

is economically justified, particularly when combined with measles vaccine (all of these studies have been conducted in countries with coverage of more than 80%). Large-scale rubella vaccination during the last decade has drastically reduced or practically eliminated rubella and CRS in many developed countries and in some developing countries.

WHO position on rubella vaccines

The existing, internationally-licensed rubella vaccines, single or in combination with vaccines against mumps and/or measles, meet most of the above general WHO requirements, and have proved to be highly efficacious in the prevention of rubella and CRS in different parts of the world. WHO recommends the use of rubella vaccine in all countries with well-functioning childhood immunization services where reduction or elimination of CRS is considered a public health priority, and where resources may be mobilized to assure implementation of an appropriate strategy.

The global burden of CRS has been sufficiently characterized, so that priority should now be given to advocating its control and prevention. All countries should assess their rubella situation and, if appropriate, make plans for the introduction of rubella vaccination. Although detailed surveillance and cost-benefit studies are not needed in every country before implementing rubella vaccination, the choice of policy in this regard requires some baseline information on the susceptibility profile of women of childbearing age (e.g. through serological studies of women attending antenatal services). Also, surveillance for CRS (as outlined in WHO guidelines) should be initiated.

Some countries with limited resources and documented very low susceptibility rates among their young females, as also reflected in low incidence of CRS, may be well advised not to start on any large-scale vaccination against rubella.

For countries wishing to prevent the occurrence of congenital rubella infection including CRS, two approaches are recommended:

- prevention of CRS only, through immunization of adolescent girls and/or women of childbearing age; or
- elimination of rubella as well as CRS through universal vaccination of infants, surveillance and assuring immunity in women of childbearing age.

Factors to be considered when deciding which approach to take should include the level of susceptibility in women of childbearing age, the burden of disease due to CRS, strength of the basic immunization service as indicated by routine measles coverage, infrastructure and resources for child and adult immunization services, assurance of injection safety, and other disease priorities.

Countries wishing to prevent CRS should immunize adolescent girls and/or women of childbearing age. The precise target population addressed will depend on susceptibility profile, cultural acceptability and operational feasibility. The most rapid impact would be achieved by mass campaigns for women of childbearing age (and men preferably). For increased impact even men should be vaccinated. Vaccination through routine services could ultimately achieve the same protection, but after a delay during which CRS cases will still occur.

In non-vaccinated individuals, susceptibility or immunity to rubella can be ascertained only by serological tests. However, serological testing is expensive and operationally impractical, and as there is no harm in vaccinating already immune individuals, serological screening for susceptibility is not recommended before rubella vaccination.

A policy of rubella vaccination of adults is essentially free of risks of altering rubella transmission dynamics, whereas inadequately implemented childhood vaccination runs the risk of increasing the number of susceptibles among adults, including women of childbearing age, and the possibility of increased numbers of cases of CRS. Consequently, it is essential that childhood vaccination programmes achieve and maintain high levels of coverage.

To avoid the risk of affecting transmission dynamics and thereby increasing susceptibility for rubella in women of childbearing age, the degree and impact of rubella immunization of children in the private sector should be followed carefully.

Following the introduction of large-scale rubella vaccination, coverage should be recorded by age and locality. Measuring coverage in infants and young children can be done through routine systems, but extra efforts are needed to routinely assess levels of coverage in adult groups. This will enable the monitoring of programme impact over time and guide future programme activities.

Countries undertaking measles elimination should consider taking the opportunity to eliminate rubella as well, through use of MR or MMR vaccine in their childhood immunization services, and also in measles campaigns. All countries undertaking rubella elimination should ensure that women of childbearing age are immune and that routine coverage in children is sustained at over 80%.

This chapter was last published as a WHO position paper: Rubella vaccines: WHO position paper. *Weekly Epidemiological Record*, 2000, 75:161–169, and is also available on the Internet at http://www.who.int/wer/pdf/2000/wer7520.pdf.

Administration summary

Type of vaccine	Live attenuated viral
Number of doses	One given by the intramuscular or subcutaneous route as monovalent, MR or MMR
Schedule	9–11 months in countries where the disease is highly endemic, later in countries with high levels of control
Booster	Not required
Contraindications	Reaction to previous dose; pregnancy (in practice, rubella vaccine given inadvertently to pregnant women has not resulted in abnormalities, indicating that termination would not be appropriate in such cases).
Adverse reactions	Malaise, fever, rash 5–12 days later; rarely arthritis, anaphylaxis
Special precautions	None

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Tetanus toxoid vaccine

Public health strategies

Tetanus is acquired through environmental exposure to the spores of *Clostridium tetani*, which are universally present in the soil. The disease is caused by the action of a potent neurotoxin produced during the anaerobic growth of the bacterium in dead tissues, e.g. in dirty wounds or in the umbilicus following non-sterile delivery. Tetanus can be prevented by immunization with tetanus toxoid, and maternal and neonatal tetanus can be prevented by immunizing women before delivery and by promoting clean delivery services and cord-care practices.

WHO perspective

Prevention of tetanus in all age groups

Protection against tetanus is acquired through administration of tetanus toxoid-containing vaccines (TT, DTP, DT, Td) and can begin before birth, continue in the neonatal period, and be sustained by reinforcing doses given to older individuals. DTP should be administered at 6, 10 and 14 weeks of age for the prevention of tetanus. Where resources permit, an additional dose of DTP should be given approximately one year after completion of the primary doses. Some countries provide a fourth dose of DTP at 18 months to four years of age. However, the need for additional booster doses of DTP, DT or Td should be addressed by individual national programmes. In countries where pertussis is of low incidence, the paediatric form of bivalent diphtheria–tetanus vaccine (DT) may be used to boost immunization in preschool children. Bivalent boosters given to children aged seven years and over and to adolescents and adults must contain a reduced diphtheria component (Td) to avoid reactions. As with diphtheria control, there is some evidence that one booster dose for adults may be inadequate, but a regimen of routine Td boosters approximately every 10 years seems ideal for maintaining immunity.

Prevention of neonatal tetanus

Neonatal tetanus is still a major global public health problem. Despite increasing coverage of women of childbearing age with at least two doses of tetanus toxoid in many countries, it is estimated that 238 000 cases of neonatal tetanus occurred in 2000, often with a very high case-fatality rate. Neonatal tetanus continues to be seriously underreported, since the populations at highest risk tend to live in rural areas and have the poorest access to health care and birth registration.

Table 7. Tetanus toxoid immunization schedule for women of childbearing age and pregnant women without previous exposure to TT, Td or DTP†

Dose of TT or Td	When to give	Expected duration of protection*
1	At first contact or as early as possible in pregnancy	None
2	At least 4 weeks after TT 1	1–3 years
3	At least 6 months after TT 2 or during subsequent pregnancy	At least 5 years
4	At least one year after TT 3 or during subsequent pregnancy	At least 10 years
5	At least one year after TT 4 or during subsequent pregnancy	For all childbearing years and possibly longer

† *Increasing numbers of women have documentation of prior receipt of vaccines containing tetanus toxoid e.g. in early childhood or at school age. As the women reach childbearing age the incidence of maternal and neonatal tetanus is expected to decline further: three properly spaced doses of DTP given in childhood are considered equivalent in protection to two doses of TT/Td given in adulthood.*

* *Recent studies suggest that the duration of protection may be longer than indicated in the table. This matter is currently under review.*

In view of the significant disease burden, all Member States of WHO, UNICEF and UNFPA have agreed on a target of eliminating maternal and neonatal tetanus as a public health problem by the year 2005. In this context, elimination is defined as a rate of neonatal tetanus below 1 per 1000 live births per year at the district level. In order to protect neonates, women should receive a minimum of two doses of tetanus toxoid vaccine at least four weeks apart, and the final dose should be given at least two weeks before delivery (table 7). This measure is additional to the use of clean practices during delivery and the care of the infant's umbilical cord. The protection of the neonate against neonatal tetanus is determined by the immunization status of the mother. A three-dose course of TT or Td provides protection against maternal and neonatal tetanus for at least five years.

From a programmatic point of view, previously unimmunized women should receive two doses of TT or Td during their first pregnancy and one dose of TT or Td during each subsequent pregnancy up to a maximum of five doses. Protective antibody levels are attained in 80%–90% of individuals after the second dose and in 95%–98% of women after the third dose. Fourth and fifth doses of TT or Td given later prolong the duration of immunity for many more years (table 7). Td is preferable as it has the added benefit of boosting protection against diphtheria.

Eliminating maternal and neonatal tetanus

The present aim is to eliminate maternal and neonatal tetanus as a public health problem in every district of every country by 2005. Elimination strategies include the following.

To achieve elimination:

- Supplementary immunization activities are conducted in order to vaccinate at least 90% of women of childbearing age with three properly spaced doses of tetanus toxoid in high-risk districts/areas where women have not been sufficiently reached by routine immunization services.
- Clean delivery practices achieved through improved training of birth attendants, distribution of clean delivery kits and improved access to health care.

To maintain elimination:

- Elimination is maintained in former high-risk districts by strengthening routine vaccination at antenatal clinics and fixed facilities and by conducting outreach activities and school-based immunization.
- School-based immunization is an effective approach to maintaining continued protection of individuals against tetanus and to boosting anti-tetanus immunity levels in females before their first pregnancy. Doses given as from the time of school entry should be of Td vaccine (or TT if Td is not available) and should be administered to both boys and girls. School-based immunization is best implemented where school enrolment and attendance rates are high.
- Clean delivery practices are further extended.
- Continued surveillance activities.

Administration summary

Type of vaccine	Toxoid as DTP, DT, TT or Td
Number of doses	At least three primary doses given by the intramuscular route
Schedule	6, 10 and 14 weeks of age*. See table 7 for schedule in pregnancy
Booster	DTP 18 months to four years of age**; TT/Td every 10 years
Contraindications	Anaphylactic reaction to previous dose
Adverse reactions	Mild local or systemic reactions are common and increase in frequency with increasing numbers of doses, and may constitute a contraindication to further doses
Special precautions	Reduced diphtheria (Td instead of DT) content as from seven years of age

* There is considerable variation between national immunization schedules in the timing of the three primary doses.

** WHO recommends that, where resources permit, an additional dose of DTP be given approximately one year after completion of the primary doses. However, the need for additional booster doses of DTP, DT or Td should be addressed by individual national programmes.

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Typhoid vaccine

Summary and conclusions

Typhoid fever is a serious systemic infection caused by the enteric pathogen *Salmonella typhi*. The infection is spread by the faecal-oral route and closely associated with poor food hygiene and inadequate sanitation. In disease-endemic areas schoolchildren and young adults are most frequently affected.

During recent decades typhoid fever has largely disappeared from industrialized countries, but remains a serious public health problem in several Asian regions of the former USSR, in parts of South-East Asia, Africa and South America. According to WHO estimates, 16 million cases occur each year, including about 600 000 deaths. Asymptomatic intestinal carriers of *S. typhi* are common in disease-endemic areas, and are important sources of infection. Antimicrobial treatment of typhoid fever and of asymptomatic salmonella carriers has become increasingly complicated by the emergence of multidrug-resistant strains of *S. typhi*.

Vaccination of high-risk populations is considered the most promising strategy for the control of typhoid fever. The old, heat-inactivated whole-cell vaccine showed protective efficacy rates that, in controlled studies, ranged between 51% and 67%, but this vaccine is associated with frequent adverse reactions. For this reason it has been replaced by newer typhoid vaccines in industrialized countries. Two currently-licensed typhoid vaccines confer protective efficacy rates comparable to those of the whole-cell vaccine, without significant side-effects. One is a parenteral vaccine based on the purified Vi polysaccharide of *S. typhi*. The other, Ty21a, is a live, attenuated vaccine that is administered orally. Following administration according to their respective schedules, both vaccines induce protective immunity for several years. Although well-controlled effectiveness trials in this field are relatively scarce, such studies in schoolchildren suggest that large-scale vaccination of selected groups against typhoid fever may be a significant step towards control of this disease.

Public health impact

Typhoid fever is caused by *Salmonella enterica*, serovar Typhi, a highly virulent and invasive enteric pathogen traditionally referred to as *Salmonella typhi*. Only humans are affected, and most often, acquisition of *S. typhi* occurs via ingestion of food or water contaminated with excreta from carriers of the bacterium. WHO conservatively estimates the annual global incidence of typhoid fever at 0.3%, corresponding to about 16 million cases, of which approximately 600 000 end in death. In some developing countries of Asia and Africa the annual incidence may reach 1% with case fatality rates as high as 10%. About 70% of all fatalities from typhoid

fever occur in Asia. Hospital-based data and passive surveillance studies in endemic areas have shown that the incidence of typhoid fever peaks between the ages of 5 and 12 years. In children under two years of age the clinical course of the disease tends to be mild and the correct diagnosis may often be missed in this age group. However, a recent community-based prospective surveillance study from India shows that the incidence of typhoid fever may peak as early as one to five years of age. Further clarification of the age-specific epidemiology in areas of high endemicity is required. Improved living conditions and the introduction of antibiotics in the late 1940s resulted in a drastic reduction of cases and mortality due to typhoid fever in industrialized countries. However, the disease is still a significant public health problem in many parts of South and East Asia, Africa and South America. In 1996–1998 a large outbreak of typhoid fever occurred in Tajikistan, causing more than 24 000 cases. An increasing number of cases has recently been reported from neighbouring Uzbekistan.

Currently, antibiotic therapy may considerably reduce mortality caused by typhoid fever. However, in recent years *S. typhi* has gradually acquired resistance to the oral antibiotics that are most widely available for its treatment, including chloramphenicol, trimethoprim-sulfamethoxazole, ampicillin and tetracycline. Thus, in Viet Nam 89%–93% of *S. typhi* strains are reported to be multidrug-resistant and in Tajikistan antimicrobial resistance of *S. typhi* is now extending to new drugs such as third-generation cephalosporins and quinolones.

The socioeconomic impact of typhoid fever in disease-endemic areas is difficult to assess, but likely to be considerable. In the United States the estimated direct medical costs associated with a case of this disease vary between US $2500 and US $4500.

The pathogen and the disease

Salmonella is a genus of the family Enterobacteriaceae. *Salmonellae* are rod-shaped, Gram-negative, non spore-forming, facultative anaerobic bacteria, and most strains are motile by peritrichous flagella (H antigen). *S. typhi* is taxonomically designated as *Salmonella enterica*, subspecies *enterica*, serovar Typhi. In addition to the H antigen, two polysaccharide surface antigens aid in the further characterization of *S. enterica*. One is the somatic O antigen involved in serogrouping (*S. typhi* belongs to serogroup D). The other is the Vi (virulence) capsular antigen that is associated with resistance to complement-mediated lysis and resistance to complement activation by the alternate pathway.

Following ingestion the bacterium may reach the reticuloendothelial system and multiply intracellularly within macrophages, a property that seems dependent on the presence of the Vi antigen. After 5–21 days of incubation the patients experience fatigue, headache, abdominal pain and fever. Constipation usually occurs in older children and adults whereas diarrhoea may occur in younger children. Severe forms of typhoid fever may entail cerebral dysfunction, delirium and shock, and occasionally intestinal perforation and haemorrhages. Immunocompromised persons and individuals suffering from achlorhydria are susceptible to lower infectious doses of *S. typhi* and are at increased risk of severe disease. Regardless of treatment or risk factors, the overall fatality rate is about 4%. Approximately 1%–4% of the patients continue to harbour *S. typhi* in their intestinal tract and gall bladder for months or years (chronic carriers).

The definitive diagnosis of typhoid fever requires the isolation of *S. typhi* from patient material. Given that blood, intestinal secretions as well as bone marrow are cultured, more than 90% of the patients will be culture-positive in the early stages of disease. Culturing blood only reduces sensitivity to 50%–70%. A chronic carrier state can be distinguished from recent infection by the serological response to the Vi polysaccharide, since carriers often have very high antibody titres to this antigen.

Chloramphenicol was for a long time the preferred treatment for typhoid fever, but owing to the development of bacterial resistance during the 1970s and 1980s, this drug was widely replaced by ampicillin and co-trimoxazole. More recently, increasing resistance to the latter antibiotics has prompted the use of quinolone derivatives and third-generation cephalosporins.

Protective immune response

Usually typhoid fever results in lifelong immunity. Reinfections are rare, at least in cases where the primary infection was not aborted by early antibiotic treatment. Immunological protection against typhoid fever is thought to require both cell-mediated and humoral responses. Following natural infection, specific antibodies are detected both in serum and in the intestines. Animal studies suggest that in the intestines, O-antigen specific secretory IgA may have an important role. Specific cytotoxic T lymphocyte (CTL) activity has been demonstrated after oral vaccination with live attenuated *S. typhi*, indicating a role for CTLs in the defence against typhoid fever.

The justification for vaccine control

As humans are the only source of infection, and transmission of *S. typhi* is by the faecal-oral route, control measures should include improved sanitation and food hygiene. Unfortunately, improvements in this field are closely linked to socioeconomic progress, which has been relatively slow in most disease-endemic areas. In addition, man-made and natural disasters frequently force people to live in unsanitary conditions favouring the emergence and spread of enteric pathogens.

In theory, control of typhoid fever may be achieved by adequate antimicrobial treatment of both clinical cases and asymptomatic faecal excreters of *S. typhi*. This approach requires well-functioning medical services, including access to the relevant drugs and reliable diagnostic laboratories, all of which are currently unavailable in the areas of highest endemicity. In addition, rapid development of microbial drug resistance significantly reduces the possibility of containing the spread of the infectious agent. Further liberal use of antibiotics will accentuate these problems. Hence, until socioeconomic development has changed the living conditions of the populations most affected, efficacious and affordable vaccines are required to control typhoid fever.

Typhoid vaccines

During the past 15 years, two new typhoid vaccines have been licensed and widely used globally, one for parenteral and the other for oral application. These vaccines have largely replaced the old and highly reactogenic heat-phenol inactivated whole-cell vaccine in many countries.

(i) The Vi polysaccharide vaccine

This vaccine is composed of purified Vi polysaccharide from *S. typhi.* It is administered subcutaneously or intramuscularly as one dose of 25 mg to individuals under two years of age. The vaccine confers protection seven days after injection. Recommended storage temperature is between +2°C and +8°C.

A randomized trial in Nepal involving persons aged 5–44 years showed 75% protection against culture-positive typhoid fever during the 20 months of active surveillance. In a recent study in South Africa, 55% efficacy was demonstrated three years after immunization of children aged 5–16 years. Ten years after vaccination, 58% still had >1mg ml^{-1} of anti-Vi IgG in their sera, a level frequently regarded as protective, although no consensus exists in this regard. However, a similar percentage of the controls had acquired the same levels of anti-Vi IgG over the 10-year period. Nevertheless, in areas of high endemicity the vaccine protected school-age children, usually considered the most susceptible age group. In regions of low disease endemicity, the duration of protection is uncertain. The vaccine is not effective in children under two years of age, and a study in Indonesia indicates that owing to poor responses, the vaccine is not cost-effective in children two to five years of age.

To maintain protection, revaccination is recommended every three years. The Vi vaccine can be given simultaneously with other vaccines relevant for international travellers such as the vaccines against yellow fever and hepatitis A. There are no contraindications other than prior severe reaction to vaccine components. Although the vaccine is safe for HIV-infected persons, the induction of protective antibodies is directly correlated to the levels of CD4 positive T-cells. Adverse reactions seem limited to fever (0%–1%), headache (1.5%–3%) and erythema or induration of more than 1 cm at the site of injection (7%). As with many other pure polysaccharide vaccines, no booster effect indicative of an immunological memory is observed. For this reason, protein-Vi polysaccharide conjugate vaccines are being developed.

(ii) The Ty21a vaccine

This is a live attenuated strain of *S. typhi* Ty21a that was developed in the early 1970s by chemical mutagenesis. Protection is markedly influenced by the number of doses and their spacing. When the vaccine is given in three doses two days apart, protective immunity is achieved seven days after the last dose. In disease-endemic areas a booster dose is recommended every three years. Travellers from non-endemic to disease-endemic regions are recommended a booster on a yearly basis. There are currently no field trial data to document the efficacy of this vaccine in children under three years of age.

The vaccine is usually administrated orally as enteric-coated capsules and is registered for use from six years of age. It has shown a protective efficacy of 62% for at least seven years after the last dose and a trial involving more than 200 000 schoolchildren in Chile demonstrated the practical utility of this vaccine. A liquid formulation of the Ty21a vaccine can be taken by children as young as two years of age and has proved more immunogenic than the capsular formulation. Currently marketed in a small number of countries, it is expected to progressively replace the enteric-coated capsule formulation. In a field trial in Chile among more than 36 000 vaccinees aged 5–19 years, this formulation provided 79% efficacy, even up to five years after immunization.

Ty21a is remarkably well tolerated. The vaccine may be given simultaneously with other vaccines, including live vaccines against polio, cholera and yellow fever, or the measles, mumps and rubella (MMR) combination. Proguanil or antibiotics should be avoided during the three days before vaccination and afterwards. It is not known whether this live attenuated vaccine can cause fetal harm when administered to pregnant women. Ty21a can be administered to HIV-positive, asymptomatic individuals without risk as long as the T-cell count (CD4) is above 200/mm^3. The vaccine requires storage between +2°C and +8°C.

Aiming at the development of more immunogenic oral vaccines against typhoid fever, several attenuated strains of *S. typhi* other than Ty21a have been tested, or are currently undergoing testing.

(iii) The inactivated whole-cell vaccine

Primary immunization with this parenteral vaccine consists of two doses given four weeks apart; a single booster dose is recommended every three years. It is still available in several developing countries and is reasonably priced. In controlled trials the inactivated whole-cell vaccine has reached protective efficacy rates of 51%–67%. However, in field trials the vaccine has been associated with fever and systemic reactions in 9%–34% of the recipients, and with short absences from work or school in 2%–17% of cases. Apart from rare anaphylactic reactions, vaccine-induced fatalities or chronic disabling conditions have not been reported.

WHO position on typhoid vaccines

The old, heat inactivated whole-cell vaccine may not always be manufactured according to international standards, whereas both the parenteral Vi-based polysaccharide vaccine and the live attenuated oral Ty21a vaccine are of assured quality and safety. The respective duration of protection is not fully established for any of these vaccines. Because of its considerable reactogenicity, the inactivated whole-cell vaccine should now be replaced by the less reactogenic and equally efficacious modern vaccines. However, for mainly economic reasons the old vaccine is still used in some parts of the world.

The current formulations at least of the Vi and Ty21a vaccines are only moderately efficient (50%–70%) in the traditional target groups of children of under five years and young adults. In children younger than three to five years of age the corresponding efficacy is insufficiently documented. Although typhoid fever is not considered a public health problem during the first years of life, recent work shows that at least in some disease-endemic areas the highest incidence of typhoid fever is found among children under five years of age. Should these findings be confirmed in other areas of high endemicity, vaccination of this age group may become more important than previously appreciated and they will have consequences for future vaccine composition as well as for the vaccination schedule. Also, as these vaccines induce different mechanisms of protection, studies of potential complementary effects should be conducted.

Neither the Vi-based polysaccharide vaccine nor the Ty21a vaccine is licensed for children under two years of age. With their current formulations they are not considered candidates for inclusion into large-scale vaccination programmes in this age group. However, while waiting for improved vaccines against typhoid fever, further assessment of the protective efficacy of the currently-licensed vaccines in the youngest age groups seems warranted.

National decisions concerning strategies to control typhoid fever should be based on thorough analyses of age-specific incidence, on groups at particular risk of infection and on cost-benefit aspects of the planned control measures.

Immunization of school-age children and young adults is recommended in areas where typhoid fever in these age groups is a significant public health problem, and particularly where antibiotic-resistant *S. typhi* strains are prevalent. In those settings immunization against typhoid fever will be required until socioeconomic improvements finally interrupt transmission of *S. typhi*. Where appropriate the use of typhoid vaccines should be harmonized with the administration of tetanus and diphtheria vaccines.

For the occasional small-scale vaccination in countries of low typhoid endemicity and for individual protection of short-term visitors to areas of high endemicity, either of the two modern vaccines is recommended. It should be noted, however, that the vaccines do not provide complete protection and should not replace hygiene precautions.

This chapter was last published as a WHO position paper: Typhoid vaccines. WHO position paper. *Weekly Epidemiological Record*, 2000, 75:257–264, and is available on the Internet at http://www.who.int/wer/pdf/2000/wer7532.pdf.

Administration summary

Type of vaccine	Oral Ty21a and injectable Vi conjugate polysaccharide (ViCPS)
Number of doses	Three doses of oral Ty21a vaccine given at two-day intervals as liquid or enteric coated capsules; one dose of ViCPS intramuscularly
Booster (travellers)	Every year for travellers to disease-endemic countries and every three years for those living in disease-endemic areas where the oral vaccine is used; every three years for the ViCPS vaccine
Adverse reactions	None significant
Contraindications	Hypersensitivity to previous dose
Special precautions	Stop proguanil, mefloquine and antibiotics three days* before starting Ty21a until one week afterwards; ViCPS given to children under two years of age does not confer long-lasting protection

* 12 hours in the United States.

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Varicella vaccine

Summary and conclusions

Varicella (chickenpox) is an acute, highly contagious viral disease with worldwide distribution. While mostly a mild disorder in childhood, varicella tends to be more severe in adults. It may be fatal, especially in neonates and in immunocompromised persons. Varicella-zoster virus (VZV), the causative agent, shows little genetic variation and has no animal reservoir. Following infection, the virus remains latent in neural ganglia, and upon subsequent reactivation VZV may cause zoster (shingles), a disease mainly affecting the elderly and immunocompromised persons. Although individual cases may be prevented or modified by varicella-zoster immune globulin or treated with antiviral drugs, control of varicella can be achieved only by widespread vaccination. Varicella vaccines based on the attenuated Oka-strain of VZV have been marketed since 1974, and the positive results of extensive safety, efficacy and cost-effectiveness analyses have warranted the introduction of these vaccines into the childhood immunization services of several industrialized countries. After observation of study populations for periods of up to 20 years in Japan and 10 years in the United States, more than 90% of immunocompetent persons who were vaccinated as children were still protected from varicella.

Information concerning several aspects of varicella vaccination is still incomplete. The duration of protection against varicella and zoster without natural exposure to the virus, the epidemiological impact of childhood vaccination at various levels of coverage, and the zoster-preventive effect of vaccination of adults and elderly people with a history of varicella need to be better understood. Furthermore, there is little information from developing countries on the disease burden of varicella and zoster, and on the incidence and impact of secondary infections. It is unlikely, however, that varicella will be among the priority vaccine-preventable diseases in most developing regions.

Decision-makers considering the use of varicella vaccine in routine immunization services must take into account the epidemiology and the public health and socioeconomic impact of varicella relative to other health concerns competing for scarce resources. The following recommendations reflect current evidence, and are likely to be modified as additional information becomes available.

- Most developing countries have other vaccine-preventable diseases that cause significantly greater morbidity and mortality, and varicella vaccine is not a high priority for routine introduction into their national immunization services.
- Routine childhood immunization against varicella may be considered in countries where this disease is a relatively important public health and socioeconomic problem, where the vaccine is affordable, and where high (85%–90%) and sustained vaccine coverage can be achieved. (Childhood immunization with lower coverage could theoretically shift the epidemiology of the disease and increase the number of severe cases in older children and adults.)
- Additionally, the vaccine may be offered in any country to individual adolescents and adults without a history of varicella, in particular to those at increased risk of contracting or spreading the infection. This use in adolescents and adults entails no risk of an epidemiological shift, as childhood exposure to VZV remains unaffected.

Public health impact

Varicella is a highly communicable viral disease with worldwide distribution. In temperate climates of the Northern Hemisphere, varicella occurs mainly in the period from late winter to early spring. Secondary attack rates reach close to 90% in susceptible household contacts. Varicella-zoster virus (VZV) is the causative agent and is transmitted by droplets, aerosol or direct contact, and patients are usually contagious from a few days before rash onset until the rash has crusted over. Once a case has occurred in a susceptible population, it is very hard to prevent an outbreak. As subclinical infection is rare, the disease is experienced by almost every human being. Sometimes, mild clinical infections may not be recognized or may be misdiagnosed. Thus, in temperate regions the majority of adults with a negative history for varicella are seropositive when tested.

In temperate climates most cases occur before the age of 10. The epidemiology is less well understood in tropical areas, where a relatively large proportion of adults in some countries are seronegative. Varicella is characterized by an itchy, vesicular rash, usually starting on the scalp and face, and initially accompanied by fever and malaise. As the rash gradually spreads to the trunk and extremities, the first vesicles dry out. It normally takes about 7–10 days for all crusts to disappear.

Although varicella is usually a benign childhood disease, and rarely rated as an important public health problem, the course may occasionally be complicated by VZV-induced pneumonia or encephalitis, sometimes resulting in persistent sequelae or death. Disfiguring scars may result from secondary bacterial infections of the vesicles, and necrotizing fasciitis or septicaemia may occur from such infections. In Canada and the United States, invasive group A streptococcal infections complicating varicella have been described with increased frequency. Other serious manifestations include VZV-induced pneumonitis (more commonly in adults), the rare congenital varicella syndrome (caused by varicella during the first 20 weeks of pregnancy) and perinatal varicella of newborns whose mothers develop chickenpox from five days before delivery to 48 hours afterwards. In patients suffering from immunodeficiencies, including HIV infection, varicella tends to be severe and zoster may be recurrent. Severe and fatal varicella may also occur occasionally in children

taking systemic steroids for treatment of asthma. In general, complications as well as fatalities from varicella are more commonly observed in adults than in children. Case-fatality ratios (deaths per 100 000 cases) in healthy adults are 30–40 times higher than among children five to nine years of age. Hence, if a vaccination programme is undertaken, it is important to ensure high vaccination coverage in order that prevention programmes do not cause changes in the epidemiology of varicella resulting in higher incidence rates in adults.

In about 10%–20% of the cases, varicella is followed later in life by herpes zoster, or shingles, a painful vesicular rash with dermatomal distribution. Most cases of zoster occur after the age of 50 or in immunocompromised persons. It is a relatively common complication in HIV-positive persons. Zoster may occasionally result in permanent neurological damage such as cranial nerve palsies and contralateral hemiplegia, or in visual impairment following zoster ophthalmia. Nearly 15% of zoster patients have pain or parasthesias in the affected dermatome for at least several weeks and sometimes permanently (postherpetic neuralgia). Disseminated, sometimes fatal zoster may occur in patients suffering from malignancies, AIDS or other conditions associated with immunodeficiency. Transmission of VZV from zoster patients may cause varicella in non-immune contacts.

The pathogen

VZV is a double-stranded DNA virus belonging to the herpesvirus family. Only one serotype is known, and humans are the only reservoir. VZV enters the host through the nasopharyngeal mucosa, and almost invariably produces clinical disease in susceptible individuals. The incubation period is usually 14–16 (10–21) days. Following varicella, the virus persists in sensory nerve ganglia, from where it may later be reactivated to cause zoster. Serum antibodies against viral membrane proteins and glycoproteins are utilized in diagnostic tests, but are less reliable as correlates of immunity, particularly to zoster. As with other human herpesviruses, nucleoside analogues such as acyclovir inhibit the replication of VZV, although less efficiently than in the case of *Herpes simplex*.

Immune response

Natural infection induces lifelong immunity to clinical varicella in almost all immunocompetent persons. Newborn babies of immune mothers are protected by passively acquired antibodies during their first months of life. Temporary protection of non-immune individuals can be obtained by injection of varicella-zoster immune globulin within three days of exposure. The immunity acquired in the course of varicella prevents neither the establishment of a latent VZV infection, nor the possibility of subsequent reactivation as zoster. Although antibody assays are conveniently used as an indication of previous infection or response to vaccination, failure to detect antibodies against VZV does not necessarily imply susceptibility, as the corresponding cell-mediated immunity may still be intact. On the other hand, about 20% of persons aged 55–65 show no measurable cell-mediated immunity to VZV in spite of persisting antibodies, and a history of previous varicella. Zoster is closely correlated to a fall in the level of VZV-specific T-cells, and an episode of zoster will reactivate the specific T-cell response.

The justification for vaccine control

Except for vaccination, no countermeasures are likely to control the dissemination of varicella or the frequency of zoster in a susceptible community. Varicella-zoster immune globulin and antiherpesviral drugs are very costly, and mainly applied for post-exposure prophylaxis or the treatment of varicella in persons at high risk of severe disease. Due to its extremely contagious nature, varicella is experienced by almost every child or young adult in the world. Each year from 1990 to 1994, prior to availability of varicella vaccine, about 4 million cases of varicella occurred in the United States. Of these cases approximately 10 000 required hospitalization and 100 died. Although varicella is not commonly perceived as an important public health problem, the socioeconomic consequences in industrialized countries of a disease that affects practically every child and causes the carer to be absent from work should not be underestimated.

The recently marketed varicella vaccines have been shown to be safe and effective. From a societal perspective, a recent cost-benefit analysis in the United States showed that routine chickenpox vaccination is likely to save five times the investment. Even when only direct costs were considered, benefits almost balanced the costs. Similar studies from developing countries are not available. However, the socioeconomic aspect of varicella is likely to be of less importance in countries with a different social organization. On the other hand, the public health impact of varicella and zoster may be increasing in regions with high rates of HIV endemicity.

It is not yet sufficiently documented that the varicella vaccine, administered either in childhood or in adult populations, will protect against zoster. However, several indications, including the results of vaccination studies in certain immunodeficient groups, are encouraging in this regard. The public health as well as the socioeconomic impact of this vaccine would increase drastically if it was proved to protect against zoster in the general population. In industrialized countries considerable amounts are spent on medical care in complicated cases of zoster in immunocompromised or elderly persons, and the increasing incidence of zoster in HIV-affected areas is well documented.

Varicella vaccines

The currently marketed varicella vaccines are based on the so-called Oka strain of VZV, which has been modified through sequential propagation in different cell cultures. Various formulations of such live, attenuated vaccines have been tested extensively and are approved for use in Japan, the Republic of Korea, the United States and several countries in Europe. Some formulations are approved for use at nine months of age and older.

Following a single dose of the above-mentioned vaccines, seroconversion is seen in about 95% of healthy children. From a logistic as well as an epidemiological point of view, the optimal age for varicella vaccination is 12–24 months. In Japan and several other countries one dose of the vaccine is considered sufficient, regardless of age. In the United States, two doses, four to eight weeks apart, are recommended for adolescents and adults, in whom 78% were found to have seroconverted after the first, and 99% after the second dose of the vaccine. Children below 13 years of age receive only one dose.

Small studies, using formulations different to that currently licensed in the United States, show that when the vaccine is administered within three days after exposure to VZV, a post-exposure protective efficacy of at least 90% may be expected. Varicella in persons who have received the vaccine ("break-through varicella") is substantially less severe than the disease in unvaccinated individuals. Further studies are needed to clarify the post-exposure efficacy of the currently-licensed product, especially in outbreak situations.

When given at separate sites and with separate syringes, simultaneous vaccination of varicella with other vaccines is as safe and immunogenic as when the vaccines are given at intervals of several weeks. However, in order to induce the same immune response as the monovalent varicella vaccine, the dose of the varicella component had to be increased when included in a tetravalent vaccine with the combined measles–mumps–rubella vaccine. A multivalent vaccine is not yet licensed.

As judged from the Japanese experience, immunity to varicella following vaccination lasts for at least 10–20 years. In the United States, childhood vaccination against varicella provides 70%–90% protection against infection, and more than 95% protection against severe disease 7–10 years after immunization. From investigation of a varicella outbreak in a day care centre, post-licensure efficacy was found to be 100% in preventing severe disease and 86% in preventing all disease. The attack rate in unvaccinated susceptible children was 88%. It is likely, but as yet not proved, that some protection is also achieved against zoster. However, in Japan as well as in the United States, the vaccine coverage in the population is quite limited, and the continued circulation of wild type VZV is likely to cause post-vaccination boosting. Hence, the long-term protection induced by the vaccine alone is difficult to assess at this time.

In immunocompromised persons, including patients with advanced HIV infection, varicella vaccination is currently contraindicated for fear of disseminated vaccine-induced disease. Vaccine safety is however being evaluated in asymptomatic HIV-infected children with CD4 counts of more than 1000, and a killed varicella vaccine has been studied in VZV-positive bone marrow transplant patients where a multiple-dose schedule has been shown to reduce the severity of zoster. Furthermore, in carefully supervised trials, patients with leukaemia in remission or solid tumours before chemotherapy, and uraemic patients waiting for transplantation, have received the vaccine. In most cases, one to two doses resulted in high rates of protection, with only moderate side-effects. A significant reduction in the rate of zoster has also been recorded in these patients.

Vaccine-associated adverse events

In healthy children the adverse effects of the vaccination are limited to some local swelling and redness at the site of injection during the first hours following vaccination (27%), and in a few cases (fewer than 5%) the vaccinees experience a mild varicella-like disease with rash within four weeks. In a placebo-controlled study involving 900 healthy children and adolescents, pain and redness at the site of vaccination were the only documented adverse events following vaccination.

The vaccine was similarly well tolerated by already-immune persons who were inadvertently immunized. Rare occasions of mild zoster following vaccination show that the currently used vaccine strains may induce latency, with the subsequent risk of reactivation. Since licensure and distribution of more than 10 million doses of vaccine in the United States, the Vaccine Adverse Event Reporting System (VAERS) has received reports of encephalitis, ataxia, pneumonia, thrombocytopenia, arthropathy and erythema multiforme occurring after vaccination. These events may not be causally related and they occur at much lower rates than following natural disease.

Contraindications for varicella vaccination

These include a history of anaphylactic reactions to any component of the vaccine (including neomycin), pregnancy (due to theoretical risk to the fetus; pregnancy should be avoided for four weeks following vaccination), ongoing severe illness, and advanced immune disorders of any type. Except for patients with acute lymphatic leukaemia in stable remission, ongoing treatment with systemic steroids (for adults more than 20 mg/day, for children more than 1mg/kg/day) is considered a contraindication for varicella vaccination. A history of congenital immune disorders in close family members is a relative contraindication. Fortunately, both varicella-zoster immune globulin (VZIG) and antiviral drugs are available should persons in the immunocompromised categories receive the vaccine by mistake. Administration of blood, plasma or immunoglobulin less than five months before immunization or three weeks afterwards is likely to reduce the efficacy of the vaccine. Due to the theoretical risk of Reye syndrome, the use of salicylates is discouraged for six weeks following varicella vaccination.

WHO position on varicella vaccines

The current varicella vaccines seem to meet the above WHO guidelines as far as their use in industrialized countries is concerned. However, from the global perspective, there are limitations in terms of price and storage. For example, one of the currently available vaccines requires storage at –15°C and use within 30 minutes of reconstitution.

The likelihood that every child will contract varicella, combined with a socioeconomic structure that implies high indirect costs for each case, make varicella relatively important in industrialized countries with temperate climates. Routine childhood vaccination against this disease is estimated to be cost-effective in such areas. Limited seroprevalence studies have suggested that susceptibility to varicella is more common among adults in tropical than in temperate climates. Thus, from the public health point of view, varicella could prove to be more important in tropical regions than previously assumed, in particular in areas where HIV is highly endemic. The impact of varicella in the global context requires further investigation. On the other hand, in most developing countries, other new vaccines, including hepatitis B, rotavirus, as well as conjugated Hib and pneumococcal vaccines, have the potential for a much greater public health impact, and should therefore be given priority over varicella vaccines. Hence, at the present time WHO does not recommend the inclusion of varicella vaccination into the routine immunization services of developing countries.

Varicella vaccine may be used either at an individual level to protect susceptible adolescents and adults, or at a population level, to cover all children as part of a national immunization service. Vaccination of adolescents and adults will protect at-risk individuals, but will not have a significant impact on the epidemiology of the disease on a population basis. On the other hand, extensive use as a routine vaccine in children will have a significant impact on the epidemiology of the disease. If sustained high coverage can be achieved, the disease may virtually disappear. If only partial coverage can be obtained, the epidemiology may shift, leading to an increase in the number of cases in older children and adults. Hence, routine childhood varicella immunization services should emphasize high, sustained coverage.

Although observations in selected immunodeficient groups indicate that childhood varicella vaccination also reduces the risk of zoster, the period of observation since introduction of the vaccine is too short to permit firm conclusions about its zoster-preventive effect in the general population. Moreover, carefully conducted vaccination studies in adults and the elderly are required before recommendations may be made concerning the use of varicella vaccines for the prevention of zoster in those age groups.

Recommendations on possible use of this vaccine for persons in certain states of immunodeficiency are beyond the scope of this article. Advice is provided by several expert panels such as the Advisory Committee on Immunization Practices (ACIP) in the United States.

This chapter was last published as a WHO position paper: Varicella vaccines: WHO position paper. *Weekly Epidemiological Record*, 1998, 73:241–248, and on the Internet at http://www.who.int/wer/pdf/1998/wer7332.pdf.

Administration summary

Type of vaccine	Live attenuated virus, Oka strain
Number of doses	One dose for persons aged under 13 years; two doses in adolescents and adults four to eight weeks apart, subcutaneous
Schedule	12–24 months of age for early childhood immunization*
Contraindications	Pregnancy; reaction to previous dose (including reaction to a component such as gelatin); any advanced immune disorder or cellular immune deficiency; symptomatic HIV infection; severe illness
Adverse reactions	Mild local reaction; mild illness with rash
Special precautions	Beware of confusion between vaccine and varicella-zoster immune globulin

* Not recommended for developing countries

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Vitamin A supplementation

Public health strategies

Globally, it is estimated that 140–250 million children under five years of age are affected by vitamin A deficiency. These children suffer a dramatically increased risk of death, blindness and illness, especially from measles and diarrhoea. As part of the global call to action, the UN Special Session on Children in 2002 set as one of its goals the elimination of vitamin A deficiency and its consequences by the year 2010. The strategy to achieve this goal is to ensure that young children living in areas where the intake of vitamin A is inadequate receive the vitamin through a combination of breastfeeding, dietary improvement, food fortification, and supplementation.

Combining the administration of vitamin A supplements with immunization is an important part of this effort. Since 1987, WHO has advocated the routine administration of vitamin A with measles vaccine in countries where vitamin A deficiency is a problem. Great success and many millions of children have been reached by including vitamin A with national immunization days (NIDs) to eradicate polio. Providing immunization-linked high-dose supplementation to new mothers soon after delivery has provided a further benefit to young infants through enriched breast milk.

Provision of vitamin A supplements every four to six months is an inexpensive, quick, and effective way to improve vitamin A status and save children's lives. The Beaton Report concluded that all-cause mortality among children aged 6–59 months was reduced by 23% through vitamin A supplementation in areas where vitamin A deficiency was a public health problem. However, comprehensive control of vitamin A deficiency must include dietary improvement and food fortification in the long term.

WHO perspective

Vitamin A is essential for the functioning of the immune system and the healthy growth and development of children. Immunization contacts offer unrivalled opportunities for delivering vitamin A to children who suffer from deficiency. Studies show that vitamin A does not have any negative effect on seroconversion of childhood vaccines.

As well as routine immunization services, national immunization days for polio eradication, measles, and multi-antigen campaigns have been used safely and successfully to provide vitamin A to a wide age range of children at risk.

High-dose vitamin A should be avoided during pregnancy because of the theoretical risk of teratogenisis (birth defects). From a programmatic perspective, high-dose vitamin A supplementation must occur during the safe infertile period immediately after delivery. Accordingly, high-dose vitamin A supplementation can be provided safely to all postpartum mothers within six weeks of delivery, when the chance of pregnancy is remote. For breastfeeding mothers, the safe infertile period extends up to eight weeks after delivery. The first contact with the infant immunization services provides an excellent opportunity to supplement postpartum mothers and improve the vitamin A content of their breast milk.

There is a well-established scientific basis for the treatment of measles cases with vitamin A supplementation that is recommended by WHO as part of the integrated management of childhood illness.

The recommended doses of vitamin A supplementation for the prevention of vitamin A deficiency are indicated in table 8.

Special issues

Field trials are in progress with a view to confirming the suitability of administering vitamin A with the DTP doses during infancy.

Table 8. Potential target groups and immunization contacts in countries with vitamin A deficiency

Target group	Immunization contact	Vitamin A dose
All mothers irrespective of their mode of infant feeding up to six weeks postpartum if they have not received vitamin A supplementation after delivery	BCG, OPV-0 or DTP-1 contact up to six weeks	200 000 IU
Infants aged 9–11 months	Measles vaccine contact	100 000 IU
Children aged 12 months and older		200 000 IU
Children aged 1–4 years	Booster doses*	200 000 IU
	Special campaigns*	
	Delayed primary immunization doses*	

* The optimal interval between doses is four to six months. A dose should not be given too soon after a previous dose of vitamin A supplement: the minimum recommended interval between doses for the prevention of vitamin A deficiency is one month (the interval can be reduced in order to treat clinical vitamin A deficiency and measles cases).

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Yellow fever vaccine

Public health strategies

Yellow fever is endemic in 33 countries in Africa and 11 countries in South America. There are two modes of transmission of the yellow fever virus, the sylvatic or forest cycle and the urban cycle. Transmission begins when vector mosquitoes (*Aedes africanus* in Africa, and several species of the genus *Haemagogus* in South America) feed on non-human primates infected with the virus. The infected mosquitoes then feed on humans travelling through the forest. The greatest risk of an epidemic occurs when viraemic humans return to urban areas and are fed on by the domestic vector mosquito *Aedes aegypti*, which then transmits the virus to other humans.

A severe epidemic is most likely to occur if conditions allow the density of vector populations to increase substantially, as can happen in a rainy season. Good epidemiological surveillance can be critical in preventing an epidemic.

Yellow fever continues to be a public health concern in many countries of Africa and the Americas. It is estimated that 200 000 cases and 30 000 deaths are attributable to yellow fever annually, most of them occurring in sub-Saharan Africa, although far fewer cases than this are reported.

The main strategies to control yellow fever are based on a combination of immunization for protection against the disease and surveillance, and are outlined below:

a) Prevention

- Administering yellow fever vaccine as part of routine infant immunization*;
- Preventing outbreaks in high-risk areas through mass campaigns*;
- Control of *Aedes aegypti* in urban centres.

**Both these strategies should ensure a minimum coverage of at least 80%.*

(b) Control

- Instituting a sensitive and reliable YF surveillance system including laboratory capacity to analyse samples and confirm suspected cases.
- Emergency response to outbreaks through mass campaigns.

WHO perspective

For the 33 countries of equatorial Africa where yellow fever is endemic, which have a combined population of 508 million, the vaccine should be routinely administered at the same time as measles vaccine, i.e. around nine months of age. Immunization services and disease-reporting systems are well established in these countries, all of which are committed to the goals of measles reduction and polio eradication. Improvement in disease surveillance is expected to follow and to be sustainable. Linking yellow fever to planned polio and measles immunization activities could save thousands of lives each year.

The incorporation of yellow fever vaccine into the routine infant and child immunization schedules was recommended in 1988 by a joint WHO/UNICEF Technical Group on Immunization in Africa. It was suggested that this be done at the time of the visit for measles vaccine (at 9 to 12 months of age), thus avoiding the need for an additional visit. As at the end of 2001, 15 of the 33 at-risk countries had implemented the recommendation. At the end of 2000, 10 countries in Africa reported coverage by the age of 12 months, the estimated average being 42%. In the at-risk countries of the Americas, 204 cases and 97 deaths were reported in 1999. After this, a more aggressive implementation contributed to a significant reduction in the number of cases from the Americas (102 cases and 51 deaths in 2000, and 80 cases and 46 deaths in 2001).

Special issues

International health regulations: A yellow fever vaccination certificate is now the only vaccination certificate that should be required in international travel, and then only for a limited number of persons. Many countries require a valid international certificate of vaccination from travellers, including those in transit, arriving from infected areas or from countries with infected areas. Some countries require a certificate from all entering travellers, even those arriving from countries where there is no risk of yellow fever. Although this exceeds the provisions of International Health Regulations, travellers may find that it is strictly enforced, particularly for people arriving in Asia from Africa or South America. Vaccination is strongly advised for travellers outside urban areas of countries in zones where yellow fever is endemic, even if these countries have not officially reported the disease and do not require evidence of vaccination on entry. The actual areas of yellow fever virus activity far exceed the officially reported infected zones.

Vaccine supply: Efforts are being made to ensure an adequate supply of vaccine so as to permit routine immunization, preventive campaigns and outbreak response in countries of endemicity. Until recently the vaccine was in short supply. A global stockpile currently exists for use in emergencies.

***Contraindications*:** The vaccine is contraindicated in immune-deficient patients, in individuals allergic to eggs and before six months of age. Individuals with symptomatic HIV infection should not receive yellow fever vaccine until such time as more information is available on its safety. Some travel clinics decide whether to administer the vaccine on the basis of the CD4 count. The risk of exposure to disease must be weighed against the potential risk of the vaccine during pregnancy.

Adverse events: Very rare cases of serious adverse events, including deaths, have recently been reported. The risk to unimmunized individuals either living in or travelling to areas where there is known yellow fever transmission is far greater than the risk of having a vaccine-related adverse event. Therefore, WHO policy on yellow fever vaccination remains unchanged.

Administration summary

Type of vaccine	Live viral
Number of doses	One dose of 0.5 ml subcutaneously
Schedule	Routine immunization with measles vaccine at nine months of age
Booster	International health regulations require a booster every 10 years
Contraindications	Egg allergy; immune deficiency from medication or disease; symptomatic HIV infection; hypersensitivity to previous dose; pregnancy*
Adverse reactions	Hypersensitivity to egg; rarely, encephalitis in the very young; hepatic failure. Rare reports of death from massive organ failure (*see above*).
Special precautions	Do not give before six months of age; avoid during pregnancy

* To be weighed according to risk of exposure and term of pregnancy

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The Department of Vaccines and Biologicals was established by the World Health Organization in 1998 to operate within the Cluster of Health Technologies and Pharmaceuticals. The Department's major goal is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases.

Five groups implement its strategy, which starts with the establishment and maintenance of norms and standards, focusing on major vaccine and technology issues, and ends with implementation and guidance for immunization services. The work of the groups is outlined below.

The *Quality Assurance and Safety of Biologicals team* team ensures the quality and safety of vaccines and other biological medicines through the development and establishment of global norms and standards.

The *Initiative for Vaccine Research* and its three teams involved in viral, bacterial and parasitic diseases coordinate and facilitate research and development of new vaccines and immunization-related technologies.

The *Vaccine Assessment and Monitoring team* assesses strategies and activities for reducing morbidity and mortality caused by vaccine-preventable diseases.

The *Access to Technologies team* endeavours to reduce financial and technical barriers to the introduction of new and established vaccines and immunization-related technologies.

The *Expanded Programme on Immunization* develops policies and strategies for maximizing the use of vaccines of public health importance and their delivery. It supports the WHO regions and countries in acquiring the skills, competence and infrastructure needed for implementing these policies and strategies and for achieving disease control and/or elimination and eradication objectives.

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