Immunization policy
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1. Introduction

The first edition of the EPI document "Immunization Policy" was published almost a decade ago (EPI 1986) and has been used extensively as a basis for immunization programmes throughout the world. At that time, many programmes were in the early stages of development and global goals referred to the achievement of coverage targets. Since then, the EPI has changed its focus to the control or elimination of major childhood diseases, and new vaccines have become available, while yet others are being developed. In May 1989, the Forty-second World Health Assembly set the agenda for the EPI in the 1990s. Challenges included the reduction of measles incidence and elimination of neonatal tetanus by 1995, global eradication of poliomyelitis by the year 2000, and the achievement of 90% immunization coverage for all vaccines by the year 2000. These challenges were reinforced in the Declaration on the Survival, Protection, and Development of Children, which was endorsed at the World Summit for Children held at the United Nations in September 1990 (World Summit Child 1990).

Immunization programmes in different countries now present a broad spectrum of progress. Some countries, particularly the poorest and those affected by war or civil disturbance, continue to have low immunization coverage, while others are close to eliminating certain of the target diseases. This indicates a need for policy-making at the national level, in response to the local epidemiology of disease and in accordance with national infrastructure of health services. However, general recommendations on immunization will continue to form a wider framework for policy-making and will be of direct use in countries with limited experience in policy-making.

This document provides a review of present immunization policies recommended by WHO/EPI. Special emphasis has been devoted to principles and topics which are new, have changed since 1986, or are considered controversial. Other EPI documents such as "EPI for the 1990s" (EPI 1992a), "Revised Plan of Action for Global Measles Control" (EPI 1993b), "Plan of Action - Global Poliomyelitis Eradication by the year 2000" (EPI 1992b) and "The Immunological Basis for Immunization" (EPI 1993c) may be helpful. Reports from the annual Global Advisory Group meetings also provide information on immunization policy. Other publications review EPI vaccines and the immunization schedules used in various countries (Cutts and Smith 1994, Dudgeon & Cutting 1991, Plotkin and Mortimer 1988, Modern Vaccines 1990).
2. Vaccines used in the EPI

2.1 The target diseases

The EPI recommends that all countries immunize against poliomyelitis, diphtheria, pertussis, tetanus and measles, and that countries with a high incidence of tuberculosis (TB) infection should immunize against TB. Hepatitis B vaccine should be integrated into national immunization programmes in all countries by 1997 (EPI 1992c). Immunization against yellow fever is recommended in endemic countries. Table 1 summarises the information on the EPI target diseases which is most relevant to the design of control programmes.

**Tuberculosis**, caused by *Mycobacterium tuberculosis*, caused an estimated 2.6 million deaths worldwide in 1990. The pandemic of HIV infection and an increase in multi-drug-resistant tuberculosis bacteria have profoundly worsened the public health burden of tuberculosis.

**Diphtheria** is a bacterial infection caused by *Corynebacterium diphtheriae* (*C. diphtheriae*), transmitted person to person through close physical and respiratory contact. Like other respiratory infections, transmission is increased in overcrowded and poor socio-economic conditions. In temperate climates, prior to vaccination, respiratory diphtheria commonly affected preschool and school-age children, and deaths occurred from exotoxin-induced damage to other organs. Large epidemics occurred in Europe during and after the second world war, with an estimated one million cases and 50 000 deaths in 1943 (Stowman 1945). Nasal diphtheria may be mild and chronic carriage of the organism frequently occurs; asymptomatic infections are common. A cutaneous form of diphtheria is common in tropical countries, and may be important in transmission. Recently, large epidemics have occurred in Russia and the Ukraine (see section 4).

**Tetanus** is caused by the action of a potent neurotoxin produced during the growth of the anaerobic bacterium, *Clostridium tetani* (*Cl. tetani*), in necrosed tissues such as occur in dirty wounds, or the umbilical cord if delivery has not been clean. Tetanus has an environmental reservoir, and is not a transmissible disease. In developed countries, it affects mainly elderly persons, because younger age groups have been immunized. In developing countries, neonatal tetanus is an important cause of infant mortality. Maternal tetanus can occur by postpartum contamination of the uterus. In addition to vaccination, improving delivery care and the care of wounds are important interventions to reduce tetanus.
**Table 1. Epidemiology of the EPI target diseases**

| Disease       | Agent                    | Reservoir | Spread                                      | Transmissible period | Subclinical infection | Duration of natural immunity | Risk factors for infection                  |
|---------------|--------------------------|-----------|---------------------------------------------|----------------------|-----------------------|------------------------------|---------------------------------------------|
| Tuberculosis  | Mycobacterium tuberculosis | Humans    | Airborne droplet nuclei from sputum-positive person | As long as sputum Acid Fast Bacilli positive | Common but not important in transmission | Not known. Reactivation of old infection commonly causes disease | Low access to care Immuno-deficiency Malnutrition Alcoholism Diabetes |
| Diphtheria    | Toxin-producing bacterium (C. diphtheriae) | Humans | Close contact - respiratory or cutaneous | Usually < 2 wks Some chronic carriers | Common | Usually lifelong | Crowding Low socio-economic status |
| Tetanus       | Toxin-producing bacterium (C. tetani) | Animal intestines | Spores enter body through wounds/umbilical cord | No person-to-person transmission | No | No immunity induced by infection | Contamination of umbilical cord Agricultural work |
| Pertussis     | Bacterium (B. pertussis) | Humans | Close respiratory contact | Usually < 3 wks (starts before whoop is apparent) | Mild illness common - may not be diagnosed | Usually lifelong | 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 | Type-specific immunity lifelong | Poor environmental hygiene |
| Measles       | Virus                    | Humans | Close respiratory contact and aerosolized droplets | 4 days before until 2 days after rash | May occur, but relative importance unknown | Lifelong | Crowding Low socio-economic status |
| Yellow fever  | Virus                    | Humans | Mosquito-borne | While mosquito infectious | Common in endemic areas | Lifelong | Mosquitoes Occupation |
| Hepatitis B   | Virus                    | Humans | Perinatal; Child; child; Blood; sexual spread | Chronic carriers >30 yrs | Common, especially in infants | If develops, lifelong | HBeAg+ mother Multiple sexual partners; IVDU |

**Pertussis** (whooping cough) is a bacterial respiratory infection caused by *Bordetella pertussis* (B. pertussis). It causes a severe cough of several weeks duration, with a characteristic whoop, often with cyanosis and vomiting. In young infants the cough may be absent and disease may manifest with spells of apnoea. Many of the symptoms are thought to be caused by toxins released by *B. pertussis*, in particular the pertussis toxin (PT; also known as lymphocyte promoting factor, LPF). The role of different antigens of *B. pertussis* is relevant to the development of new vaccines, and interested readers are referred to Cherry (1992), Edwards (1993) and EPI (1993c).

**Poliomyelitis** is an acute viral infection spread via the faecal-oral route, thus transmission is higher in areas of poor sanitation. Where sanitation is good, pharyngeal spread becomes more important. The majority of wild poliovirus infections are asymptomatic; the risk of paralysis is approximately 1 in 200 infections among infants <1 year old, and 1 in 100 infections among children aged 1-14 years. Factors increasing the likelihood of paralysis include the administration of injections or tonsillectomy during the incubation period of poliovirus infection, pregnancy, stress and trauma.
**Measles** is an acute viral infection that is transmitted by close respiratory contact, and may also spread via aerosolized droplets. Most deaths occur through secondary infections of the respiratory and/or gastrointestinal tract.

**Yellow fever** is a viral haemorrhagic fever that causes an estimated 30,000 deaths each year (EPI 1992d). In the forest pattern of yellow fever, the most common in the Americas, the main host is the monkey, and man is an accidental host. In the urban pattern, man is the host and the virus is transmitted via Aedes aegypti mosquitoes from person to person. The mosquito vector breeds in small stagnant water collections and hence transmission is facilitated by poor environmental hygiene. Thirty-three countries in Africa are considered at risk of yellow fever.

A cute **hepatitis B** is caused by the hepatitis B virus (HBV). Three of the antigens of the HBV are crucial in sero-epidemiology. These are the hepatitis B surface antigen (HBsAg) which is part of the coat of the virus, the core antigen (HBcAg), and the e antigen, a product of the breakdown of the core antigen which indicates high infectivity (HBeAg). A acute infection may be subclinical, especially in infants and young children, or may present with malaise, nausea and jaundice. The main public health consequences of HBV infection are the chronic liver disease and liver cancer which arise in carriers of the HBV virus, who are identifiable through detection of HBsAg. The younger the age at infection, the higher the chance of becoming a carrier: as many as 95% of infected infants, but only around 10% of adults, become long term carriers. In developing countries, the main route of transmission is perinatally (vertical transmission) from a carrier mother to her baby, which is more likely if the mother is positive for HBVe antigen, and "horizontal" transmission between young children. In industrialized countries, the main routes of transmission are sexual intercourse (which also plays a role in central and east Africa and much of Asia), blood to blood contact (e.g., transfusion, needle sharing among intravenous drug users as well as mother to baby (Hall 1994)).

### 2.2 Vaccine preparations available

Table 2 presents general information on the nature of EPI vaccines, their potency, form and route of administration, and Table 3 summarizes information on their immunogenicity and efficacy. Bacterial vaccines include Bacille Calmette Guerin (BCG) that contains live attenuated Mycobacterium bovis (M. bovis), and pertussis vaccine that contains killed pertussis bacteria. Vaccines against diphtheria and tetanus are toxoids (detoxified bacterial toxins). Viral vaccines include measles, yellow fever and oral polio vaccine which are all live attenuated viruses. Hepatitis B vaccines are produced from the surface antigen. Some vaccines are available in a fluid form, ready for use, while others are in a freeze-dried (lyophilized) form that must be reconstituted with cool diluent prior to administration. Detailed information on the immunological basis for the use of these vaccines is provided in the EPI series of modules on the Immunological Basis for Immunization (EPI 1993c).
### Table 2. Characteristics of EPI vaccines

| Disease       | Nature of vaccine | Minimum potency per dose | Form      | Adjuvant                  | Conservant                  | No. of doses* and route | Heat stability |
|---------------|-------------------|--------------------------|-----------|---------------------------|-----------------------------|--------------------------|----------------|
| Tuberculosis  | Attenuated *M.* bovis | 50,000 to one million live particles | Freeze-dried | None                         | None                         | 1 I/D                      | Medium in dried form, low in reconstituted form |
| Diphtheria    | Toxoid            | At least 30 IU           | Fluid     | Al(OH)₃ / AlPO₄            | Usually merthiolate          | 3 I/M                      | High           |
| Tetanus       | Toxoid            | At least 40 IU in TT and 60 IU for T component in DPT when tested in mice | Fluid     | Al(OH)₃ / AlPO₄            | Usually merthiolate          | 3 I/M                      | High           |
| Pertussis     | Killed whole cell pertussis bacterium | At least 4 IU | Fluid     | Al(OH)₃ / AlPO₄            | Usually merthiolate          | 3 I/M                      | Medium         |
| Poliomyelitis | Attenuated live viruses of 3 types | Type 1: ≥ 1 million Type 2: ≥ 100 000 Type 3: ≥ 600 000 - infectious units - | Fluid     | None                         | Stabilizer: magnesium chloride or sucrose | 4 Oral                      | Low            |
| Measles       | Attenuated live virus | At least 1000 infectious units | Freeze-dried | None                         | Small amounts of antibiotics and stabilizers | 1 S/C                      | Medium in dried form, low in reconstituted form |
| Yellow fever  | Attenuated live virus | At least 1000 mouse LD₅₀ or the equivalent in PFU | Freeze-dried | None                         | Stabilizing substances       | 1 S/C                      | Medium in dried form, low in reconstituted form |
| Hepatitis B   | HBsAg             | 2.5 to 20 mcg of HBsAg   | Fluid     | Al(OH)₃ / AlPO₄            | Usually merthiolate          | 3 I/M                      | High           |

*International units of potency as determined in animal tests
Infectious units: CCID₅₀ - cell culture infective dose 50%: the quantity of a virus suspension that will infect 50% of cell cultures
PFU - plaque forming units: the smallest quantity of a virus suspension that will produce a plaque in monolayer cell cultures

* Number of doses in EPI-recommended primary schedule (see section 3); I/D : intradermal; I/M : intramuscular (some countries use deep subcutaneous injections);
S/C : subcutaneous
### Table 3. Vaccine efficacy and vaccine-induced immunity

| Vaccine | Vaccine Efficacy | Nature of protective antibodies and protective level of antibodies * | Duration of immunity after primary series | Comments |
|---------|-----------------|---------------------------------------------------------------|------------------------------------------|----------|
| BCG     | 0-80% vs TB lung 75-86% vs meningitis and miliary TB | Not known; immunological response includes cell-mediated immunity. | Unknown; some evidence that immunity wanes with time | Reasons for varying efficacy multi-factorial |
| Diphtheria toxoid | >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 | Recent trends to lower antibody levels in adults because of less natural boosting |
| Tetanus toxoid | >95% (>80% after 2 doses) | Antitoxin; 0.01 IU/ml by neutralization test | 5 years | 5 doses in adults provide over 20 yrs protection |
| Pertussis | Estimates vary widely; efficacy higher against severe disease (around 80% protection) | Immunity is probably provided by antibodies against different components of pertussis bacteria; which antibodies and what protective level are not known | Unknown; some evidence that it wanes with time | Lack immunological correlates of protection |
| Polio- limbicis | >90% 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; shorter when no wild virus circulating | Primary series may not give adequate protection in hot climates |
| Measles | >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; shorter when no wild virus circulating | Lower efficacy when maternal antibody present |
| Yellow fever | Clinical efficacy not measured; >92% seroconversion to vaccine | Neutralizing antibody; protective level not known | 10-30 years | Boosters required every 10 years for international travel |
| Hepatitis B | 75-95%; efficacy higher against chronic carriage than against infection with the virus | Antibody to surface antigen 10 mIU/ml | >10 years; further follow-up is ongoing | Efficacy lower if injected into gluteal muscle. |

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

**BCG.** Although BCG is the most widely used vaccine in the world (85% of infants received a dose of BCG in 1993), estimates of efficacy vary widely and there are no reliable immunological markers of protection against tuberculosis. Clinical efficacy in preventing pulmonary TB has ranged from zero protection in the southern United States and in Southern India/Chingleput, to approximately 80% in the UK (Fine and Rodrigues 1990). There is no consensus on the reasons for this variation. Efficacy does not depend on BCG strain or manufacturer (Milstien and Gibson 1990). Some studies suggest that efficacy is reduced if there has been prior sensitization by environmental mycobacteria, but the evidence is not consistent. The degree of protection has not correlated with the degree of tuberculin test sensitivity induced by immunization, nor with BCG scar size. Data showing that BCG protects against tuberculous meningitis and against miliary tuberculosis (estimated 75-86% protection (Rodrigues et al 1993)) have led to a hypothesis that BCG protects against bloodborne dissemination of the bacteria, but does not limit the growth of localized foci that occurs in pulmonary TB. BCG also protects...
against leprosy, although the estimated efficacy has varied from 20% in Burma to 80% in Uganda (Fine 1989). Because efficacy against pulmonary tuberculosis is doubtful, the mainstay of the tuberculosis control programme is case-finding and treatment. BCG immunization at birth, however, will reduce the morbidity and mortality from tuberculosis among children.

**Diphtheria toxoid.** Diphtheria toxoid is a formaldehyde-inactivated preparation of diphtheria toxin, adsorbed onto aluminium salts to increase its antigenicity. This toxoid protects against the action of the toxin. Immunized persons can be infected by toxin-producing strains of diphtheria, but the systemic manifestations of diphtheria do not occur. Although the public health burden of diphtheria has been low in most developing countries, because most children acquired immunity through subclinical or cutaneous infection, recent outbreaks of diphtheria have been observed in Algeria, China, Jordan, Lesotho, Sudan, and Yemen Arab Republic, showing the importance of immunizing children in all countries (Galazka et al 1995a, 1995b). Diphtheria outbreaks in adults in Europe show the need to maintain immunity against the disease throughout life (see section 5). There are no data from randomized controlled trials of the clinical efficacy of diphtheria toxoid, but outbreak investigations have shown efficacies of over 87% (Jones et al 1985).

Diphtheria toxoid is almost always administered together with tetanus toxoid and pertussis vaccine as part of DPT vaccine in the primary vaccination series. It is also available as a component of other combined vaccines, or as a monovalent vaccine. DPT vaccine contains 10-20 Lf per dose of diphtheria toxoid, and the potency of diphtheria toxoid is at least 30 IU per dose. A combined diphtheria-tetanus vaccine exists in two forms: DT, with 10 - 30 Lf per dose, intended for children 7 years of age or younger, and Td, which has a reduced amount of diphtheria toxoid (2 to 5 Lf per dose) for use in older children and adults because of hyperreactivity to diphtheria toxoid in persons already sensitized to the antigen. DT is used for children who have contraindications to pertussis vaccine, and Td is used in countries that recommend booster doses of these toxoids throughout life (see section 5.1).

**Tetanus toxoid.** Tetanus toxoid (TT) is a formaldehyde-inactivated preparation of tetanus toxin, adsorbed onto aluminium salts to increase its antigenicity. TT is stable and can withstand exposure to room temperature for months and to 37°C for a few weeks without a significant loss of potency. TT induces the formation of specific antitoxins, which neutralize the toxin. Antitoxin which passes to the foetus across the placenta following active immunization of the mother prevents neonatal tetanus. In general, a tetanus antitoxin level of 0.01 IU/ml serum, as determined by in vivo assays such as the neutralization assay, is considered the minimum protective level (EPI 1993c). The corresponding level of antibody measured by other assays may be higher, and usually 0.1 IU/ml of antibody measured by in vitro assays such as ELISA or passive haemagglutination is considered a safe estimation. TT is a highly effective vaccine, although as with all vaccines, some cases of disease occur in immunized individuals. In most studies, the efficacy of two doses of TT during pregnancy in preventing NT has ranged from 80-100% (EPI 1993c).

**Pertussis vaccine.** Two types of pertussis vaccine are available: whole cell vaccines, which contain whole pertussis bacteria killed by chemicals or heat, and acellular
vaccines, which have been introduced recently in some industrialized countries. Whole cell vaccines are effective in preventing serious illness, but they do not protect completely against infection with the organism. Efficacy and antibody levels wane with time after vaccination (Fine and Clarkson 1987). The protective level of antibodies against pertussis is not known. The degree of protection against disease has varied widely in different studies, partly because of methodological differences, and there have been very few studies in developing countries. Nonetheless, the importance of pertussis vaccination is demonstrated by the decline in reported incidence in industrialized and developing countries with well-established immunization programmes, and the rebound in incidence and recurrence of epidemics that occurred in countries such as Sweden, the UK and Japan when vaccination uptake fell (Galazka 1992). Whole cell vaccine causes frequent local reactions and fever. Rarely, it may cause neurological reactions (see section 7).

Acellular pertussis vaccines contain isolated and purified immunogenic pertussis antigens. Usually they include pertussis toxoid (pertussis toxin treated to destroy its toxicity), filamentous haemagglutinin, agglutinogens and outer membrane protein. Local reactions are much less common following acellular than whole cell pertussis vaccine. The frequency of more serious neurological events in young children has not been determined. Acellular pertussis vaccines have been used routinely in Japan since 1981 in children above two years of age and in December 1991 were licensed in the USA for booster doses of DPT in children aged 15 months through 6 years (ACIP 1992). Several clinical trials are now in progress to compare the efficacy of primary immunization of infants with DPT acellular and whole cell pertussis vaccines (Cherry 1992). Meanwhile, the widespread use of DPT vaccine containing the whole cell pertussis component remains the cornerstone of pertussis control.

**Poliomyelitis vaccines.** There are two types of vaccine against poliomyelitis: oral and injectable. Oral poliomyelitis vaccine (OPV) is composed of the three types of attenuated polioviruses (1, 2 and 3). Because of its low cost, ease of administration, superiority in conferring intestinal immunity, and the potential to infect household and community contacts secondarily, the EPI recommends trivalent OPV as the vaccine of choice for eradication of poliomyelitis.

In industrialized countries, seroconversion rates after 3 doses of OPV have been demonstrated to be high (>90%) to all 3 types of virus. Seroconversion rates have been lower in developing countries, however: 73% (range 36% to 99%) for type 1, 90% (range 71% to 100%) for type 2, and 70% (range 40% to 99%) for type 3. The efficacy of 3 doses of OPV in preventing paralytic polio in developing countries ranges from 72% to 98% when the cold chain is properly maintained (EPI 1993c). Factors that reduce the immune response in developing countries (other than cold chain problems) include interference from other enteroviruses (that may be related to seasonal differences in response), and interference between the three vaccine viruses (that may be related to the relative doses of each virus type in the vaccine formulation). In many developing countries, routine immunization alone may not be sufficient to stop transmission of wild poliovirus, and supplementary immunization activities are recommended, as described in section 5.
Concern over low seroconversion after 3 doses of OPV led to a revival of interest in inactivated polio vaccine (IPV) in some countries, either as the sole vaccine against polio or in schedules combined with OPV. An improved IPV (e-IPV, enhanced potency vaccine) has been developed and used in several European countries. A schedule of two doses of combined IPV/DPT has been used in Africa and Israel, with high seroconversion rates to polio. However, pertussis agglutinin level waned faster in a two-dose schedule group than in a three-dose group (Müller et al 1984, Swartz et al 1986, Rumke et al 1993). Although IPV suppresses pharyngeal excretion of wild poliovirus, this vaccine has only limited effects on intestinal excretion of poliovirus. The ability of IPV to eradicate poliovirus in developing countries, where faecal-oral transmission predominates, is doubtful.

**Measles vaccine.** Measles vaccines are live, further attenuated virus preparations derived from various measles virus strains isolated in the 1950s. Standard titre vaccines contain about but not less than $3 \log_{10}$ (i.e. 1000) infectious units per dose; higher potency vaccines do not increase seroresponse when administered to children aged 9 months or above. In developing countries, seroresponse rates and clinical efficacy have usually exceeded 85% (Díaz-Ortega et al 1994).

**Yellow fever vaccine.** Freeze-dried yellow fever vaccine contains the live attenuated 17D virus strain. It is highly immunogenic, over 92% of immunized children develop neutralizing antibodies that persist for at least 10 years and often 30 years or more (EPI 1993c). In 1990, the EPI Global Advisory Group recommended that all countries at risk of yellow fever should incorporate the vaccine into their EPI schedules on a routine basis (EPI 1991a). The vaccine is recommended for use from 6 months of age and is most easily integrated into the EPI by administering it at the same time as measles vaccine (usually 9 months). As of 1992, 16 of 33 countries at risk in Africa included yellow fever vaccine routinely in their immunization programmes.

**Hepatitis B vaccine.** Two types of hepatitis B vaccine containing HBsAg are available: plasma-derived vaccine and recombinant vaccine. Both vaccines are safe and immunogenic even when administered at birth (maternal anti-HBsAg antibody does not interfere with the response to the vaccine), and highly efficacious. Over 90% of susceptible children develop a protective antibody response (over 10 mIU/ml) following three doses of vaccine, and the efficacy of the vaccine in preventing chronic carriage in most cohorts of children studied for more than 10 years exceeds 90%.

Infants of HBsAg-positive carrier mothers respond less well to the vaccine since it is often delivered after infection has occurred. The vaccine efficacy in preventing chronic HBV carriage in these infants ranges from 75% to 95%. Addition of one dose of hepatitis B immune globulin (H BIG ) at birth to the vaccine schedule may improve efficacy somewhat, but use of H BIG is not feasible in most developing countries.
2.3 Administration of vaccines

Table 2 shows number of doses and route of administration of EPI vaccines.

Vaccines containing aluminium adjuvants (DPT, DT, TT, Td and hepatitis B vaccine) should be injected intramuscularly. Some Scandinavian and Eastern Europe countries practise deep subcutaneous injections of aluminium-adjuvanted vaccines, claiming a low rate of local reactions. The preferred site for intramuscular injection in infants and young children is the anterolateral aspect of the upper thigh since it provides the largest muscular mass. In older children, the deltoid muscle has achieved sufficient size to offer a convenient site for intramuscular injection. Similarly, in adult women, the deltoid is recommended for routine intramuscular administration of TT.

The buttock should not be used routinely as an immunization site for infants, children, or adults because of the risk of injury to the sciatic nerve. Since the depth of gluteal fat in adult women is usually more than 3.5 cm, which is typically the length of the injection needle, injecting vaccines into the buttock may result in depositing the vaccine in the deep gluteal fat tissue. Gluteal administration of hepatitis B and rabies vaccine in adults has been associated with an impaired immune response possibly because of inadvertent deposition into, and poor adsorption of the vaccine from, fatty tissue.

Since hepatitis B vaccine is still expensive, some authors advocate the intradermal injection of a reduced dose of this vaccine. The adequacy and reliability of this practice has not been clearly established, and the EPI does not recommend this route. The immune response following a lower dose, especially of recombinant hepatitis B vaccine, may be reduced.
3. Basic immunization schedules and strategies

3.1 Routine immunization of infants

Recommendations for the age at which vaccines are administered are influenced by several factors:

- age-specific risks of disease
- age-specific immunological response to vaccines
- potential interference with the immune response by passively transferred maternal antibody
- age-specific risks of vaccine-associated complications
- programmatic feasibility

In general, vaccines are recommended for the youngest age group at risk for developing the disease whose members are known to develop an adequate antibody response to immunization without adverse effects from the vaccine. In addition to the need to protect infants before they encounter the wild disease-causing agents, administering vaccines early in life makes it easier to achieve high immunization coverage. Table 4 shows the immunization schedule recommended by the EPI for developing countries.

### Table 4. The immunization schedule for infants recommended by the WHO Expanded Programme on Immunization

| Age  | Vaccines                  | Hepatitis B vaccine ** |
|------|---------------------------|------------------------|
|      |                           | Scheme A | Scheme B |
| Birth| BCG, OPV 0                | HB 1      |
| 6 weeks| DPT 1, OPV 1              | HB 2      | HB 1     |
| 10 weeks| DPT 2, OPV 2              |           | HB 2     |
| 14 weeks| DPT 3, OPV 3              | HB 3      | HB 3     |
| 9 months| Measles, Yellow fever*    |           |          |

* In countries where yellow fever poses a risk.

** Scheme A is recommended in countries where perinatal transmission of hepatitis B virus is frequent (eg, South East Asia). Scheme B may be used in countries where perinatal transmission is less frequent (eg sub-Saharan Africa).
The schedule calls for all children to receive one dose of BCG vaccine, 3 doses of DPT vaccine, 4 doses of OPV, and one dose of measles vaccine before the first birthday. In countries with HBsAg carriage rates of 2% or more, universal infant immunization with HB vaccine is recommended. Countries with a lower HBV prevalence may consider immunization of all adolescents as an addition or alternative to infant immunization. The rationale for this schedule is discussed below, and where relevant, reference is made to the variation in schedules in industrialized countries.

**Age at initiating vaccination.** The response to vaccines may be affected by maternal antibody transferred in-utero to the foetus, and by the maturity of the immune response. Although immaturity of the immune system reduces the response to some polysaccharide vaccines (see section 8), young infants respond adequately to the EPI vaccines. Furthermore, babies born prematurely respond adequately to the EPI vaccines without any increase in side effects (Bernbaum et al. 1984, Conway et al. 1987, 1993, Roper & Day 1988, Smolen et al. 1983). Immunization of preterm infants should begin at the same chronological age recommended for term infants (Amer. Academy Pediatr. 1991, ACIP 1994, EPI 1988).

Because BCG is thought to be most effective in preventing tuberculous meningitis and disseminated disease in infants and young children (Camargos et al. 1988, Jin et al. 1989, Miceli et al. 1988, Sirinavin et al. 1991, ten Dam 1990a, Wasz-Hochert et al. 1988), the EPI Global Advisory Group recommended in 1990 that BCG should continue to be given as soon after birth as possible in all populations at high risk of tuberculosis infection. However, further research is needed on the long-term effectiveness of BCG given in infancy. In some countries where the risk of tuberculosis infection is low, BCG vaccine is administered to school-age children. In England and Wales, for example, BCG vaccine is offered to tuberculin-negative school children at 10-13 years (Department of Health 1990), and appears to provide more than 70% protection against tuberculosis for at least 10 years (Research Committee 1980). Many countries of central and eastern Europe administer BCG at birth and give additional doses to tuberculin-negative children at later ages (see section 5); there is no evidence that multiple doses provide increased levels of protection.

Maternal antibody against most of the other EPI diseases is transferred to the foetus. Administration of DPT vaccine before one month of age results in a suboptimal response, but the first dose of DPT can be given effectively after four weeks of age (Halsey and Galazka 1985).

Antibodies to polioviruses are transmitted transplacentally. Nonetheless, among neonates who receive a dose of OPV, 70 - 100% will develop local immunity in the intestinal tract and 30 - 50% will develop serum antibodies to one or more poliovirus types. Most infants excrete the virus for less than four weeks; therefore, the administration of a single dose of OPV at birth or as late as two weeks after birth should not interfere with the dose of OPV recommended at six weeks of age. Administration of an additional dose of OPV at birth leads to higher seroconversion rates at a younger age than occur with a 3-dose schedule (De Xiang et al 1986, Weckx et al. 1992). An additional reason for providing OPV at birth and
completing the DPT/OPV series early is that older children have a higher risk of injection-associated poliomyelitis (paralysis that is provoked by the administration of injections, including DPT vaccine, while a child is in the incubation period of poliovirus infection) (EPI 1993c).

Persistent maternal antibody is a major factor determining the age for measles immunization. At age 9 months, 10 percent or more of infants in many countries still have levels of maternal antibody that interfere with the response to immunization. Delaying immunization would increase the rate of seroconversion (Halsey et al. 1985), but would result in unacceptably high levels of morbidity and mortality prior to immunization in most developing countries.

From data on the age-specific incidence of measles and age-specific seroconversion rates to measles vaccine in developing countries, immunization at age 8-9 months was predicted to lead to seroconversion in at least 85% of infants and to prevent most of the cases and deaths. The EPI recommends immunization at age 9 months in routine immunization programmes in developing countries. In situations where there is a particularly high risk of mortality among children under age 9 months, such as refugee camps, hospitalized infants, and HIV-infected infants, two doses of standard titre measles vaccine are recommended at 6 and 9 months of age. (EPI 1993d). In industrialized countries, the risk of measles disease in young children is much lower, and measles vaccine is administered at 12-15 months of age, when virtually all children have lost maternal antibody and an optimal immune response is achieved.

For yellow fever, the age at administration has been determined by age-dependent rates of adverse events and by programmatic feasibility. Yellow fever is not recommended for use prior to 6 months of age because, although neurological reactions are extremely rare, 14 of 18 cases of encephalitis that have been temporarily associated with the vaccine (following over 200 million vaccine doses delivered since 1945) were reported in children immunized at 4 months of age or younger (Meegan 1991).

The age for beginning hepatitis B immunization depends on the proportion of infections that are acquired perinatally. In South East Asia, where perinatal infection is common, it is important to administer the first dose as soon as possible after birth. The second dose is administered with DPT-1 and the third dose with DPT-3. In much of Africa, perinatal infection is less common, thus immunization can begin later. Programmatically, it is easiest if the three doses are administered at the same time as the three doses of DPT. A combined preparation of DPT and hepatitis B vaccine is likely to be available in the next 1-2 years, which will facilitate the administration of the vaccine, though countries with a high proportion of perinatal infection may still need to give monovalent HBV at birth even after the introduction of the combined vaccine.

Hepatitis B vaccine should be integrated into national immunization programmes in all countries with a hepatitis B carrier prevalence (HBsAg) of 8% or greater by 1995 and in all countries by 1997. Target groups and strategies may vary with the local epidemiology of the disease. When carrier prevalence is 2% or greater, the most effective strategy is incorporation in the routine infant immunization schedules.
Countries with lower prevalence may consider immunization of adolescents as an addition or alternative to infant immunization (EPI 1992c).

### 3.2 Interval between multiple doses of the same antigen

Some vaccines (DPT, DT, OPV, TT, hepatitis B vaccine) require administration of more than one dose for development of an adequate antibody response. Giving doses of a vaccine at less than the recommended 4 week interval may lessen the antibody response and should be avoided. If a vaccine dose is given at less than the recommended 4 week interval, it should not be counted as part of the primary series. Lengthening the interval between doses of these vaccines leads to higher antibody levels, but it is more important to complete the primary series early and protect the child before the age of high risk for infection than to aim for an optimal immune response.

 Longer-than-recommended intervals between doses do not reduce final antibody concentrations. If a dose of DPT or OPV is missed, immunization on the next occasion should be continued as if the usual interval had elapsed; no extra dose is needed (EPI 1979).

### 3.3 Simultaneous administration of vaccines

To reduce the number of contacts required to complete the immunization series, as many antigens as possible are given at a single visit. All the EPI antigens are safe and effective when administered simultaneously, i.e. during the same immunization session but at different sites (King and Hadler 1994). For example, a 1 year old child who has never previously been immunized should receive BCG, measles, and the first dose of DPT and polio vaccines (and yellow fever and hepatitis B vaccines if appropriate). The EPI does not, however, recommend mixing different vaccines in one syringe before injection, or using a fluid vaccine for reconstitution of a freeze-dried vaccine. Such practices can lead to lower potency of both vaccines. If vaccines are not given on the same day, the main potential problem is interference between two live vaccines, which should be spaced at least 4 weeks apart if not administered on the same day.

There are known examples of the erroneous use of toxic substances (such as pavulon - a curare-like drug) for reconstitution of freeze-dried (lyophilized) vaccines. It is therefore reasonable to follow strictly the principle of never, ever, reconstituting freeze-dried vaccines in anything other than the diluent supplied with them.

### 3.4 Contraindications to immunization

There are few absolute contraindications to the EPI vaccines. The risk of delaying an immunization because of an intercurrent illness is that the child may not return again and the opportunity is lost; throughout the world, missed immunization opportunities because of false contraindications are a major cause of delay in completing the schedule, or of non-immunization.

In general, the EPI recommends that health workers should use every opportunity to immunize eligible children; vaccines should be given to all eligible children
attending outpatient clinics. Children who are hospitalized should be immunized as soon as their general condition improves and at least before discharge from hospital. Measles vaccine should preferably be given on admission to hospital because of the risk of nosocomial measles transmission.

Generally speaking, live vaccines should not be given to individuals with immune deficiency diseases or to individuals who are immunosuppressed due to malignant disease, therapy with immunosuppressive agents, or irradiation. However, both measles and oral poliomyelitis vaccines should be given to persons with HIV/AIDS. Children with symptomatic HIV infection should not be immunized with BCG and yellow fever vaccines (see section 6).

A severe adverse event following a dose of vaccine (anaphylaxis, collapse or shock, encephalitis/encephalopathy, or non-febrile convulsions) is a true contraindication to immunization. Such events can be easily recognized by the mother and the health worker. A second or third DPT injection should not be given to a child who has suffered such a severe adverse reaction to the previous dose. The pertussis component should be omitted and diphtheria and tetanus immunization completed with DT vaccine. Vaccines containing the whole cell pertussis component should not be given to children with an evolving neurological disease (e.g. uncontrolled epilepsy or progressive encephalopathy).

Persons with a history of anaphylactic reactions (generalized urticaria, difficulty in breathing, swelling of the mouth and throat, hypotension, or shock) following egg ingestion should not receive vaccines prepared on hen’s egg tissues (e.g. yellow fever vaccine and influenza vaccine). Vaccine viruses propagated in chicken fibroblast cells (measles or combined measles-mumps-rubella vaccines) can usually be given to such individuals.

Table 5. Conditions which ARE NOT contraindications to immunization:

- Minor illnesses such as upper respiratory infections or diarrhea, with fever < 38.5°C
- Allergy, asthma, or other atopic manifestations, hay fever or "snuffles"
- Prematurity, small-for-date infants
- Malnutrition
- Child being breastfed
- Family history of convulsions
- Treatment with antibiotics, low-dose corticosteroids or locally acting (e.g. topical or inhaled) steroids
- Dermatoses, eczema or localized skin infection
- Chronic diseases of the heart, lung, kidney and liver
- Stable neurological conditions, such as cerebral palsy and Down's syndrome
- History of jaundice after birth
False contraindications. Many immunization programmes have long lists of contraindications, most of which are inappropriate. Table 5 shows conditions most often wrongly considered to be contraindications in Europe (EPI 1988) and the USA (ACIP 1994) as well as in developing countries. It is particularly important to immunize children suffering from malnutrition. Low grade fever, mild respiratory infections and other minor illnesses should not be considered as contra-indications to immunization (Galazka et al. 1984). Diarrhoea should not be considered a contraindication to OPV.

3.5 Missed opportunities

A missed opportunity for immunization occurs when a child or woman of childbearing age comes to a health facility or outreach site and does not receive any or all of the vaccine doses for which he or she is eligible. A review of 79 missed opportunity studies from 45 countries identified the following most important reasons for missed opportunities:

(1) the failure to administer simultaneously all vaccines for which a child was eligible;

(2) false contraindications to immunization;

(3) health worker practices, including not opening a multi-dose vial for a small number of persons to avoid vaccine wastage; and

(4) logistical problems such as vaccine shortage, poor clinic organization and inefficient clinic scheduling (Hutchins et al. 1993).

To reduce missed opportunities, all health facilities seeing women and children should offer immunization services as frequently as possible, with appropriate immunization schedules. The immunization status of all children in the target age group should be screened routinely and immunization should be provided at every opportunity. Health workers should be taught which are true and which are false contraindications, and supervisors should monitor compliance with recommendations, for example using the EPI training module on missed opportunities (EPI 1991b).

3.6 Prevention of neonatal tetanus by immunizing women with tetanus toxoid

The optimal programme to protect newborns against neonatal tetanus via immunization of their mothers depends on the immunization history among women.

When most women of childbearing age have not previously been immunized with TT in their infancy or adolescence, implementation of a TT five-dose schedule for women of childbearing age is of the utmost importance (Table 6). Each country should define the age group to be included in the "childbearing age" category (eg: 15-44 years, 15-35 years, etc) according to local fertility patterns and the available resources. In practice, this scheme will also be used in areas where there is little or
no documentation of past immunization with tetanus-containing vaccines, even if some women are likely to have received some doses in childhood.

This TT immunization schedule should include a first dose given at the first contact, a second dose at least 4 weeks after the first dose, and a third dose given 6 - 12 months after the second dose (Table 6). Protective antibody levels are attained in 80-90% of women after the 2nd dose, and in 95-98% of women after the 3rd dose. This basic course will provide protection for at least 5 years. Fourth and fifth doses of TT given later will prolong the duration of immunity for 10 and 20 years, respectively.

**Table 6. Tetanus toxoid immunization schedule for women of childbearing age**

| Dose | When to give                                      | Expected duration of protection |
|------|---------------------------------------------------|---------------------------------|
| TT 1 | at first contact or as early as possible in pregnancy | none                            |
| TT 2 | at least 4 weeks after TT 1                        | 1 - 3 years                     |
| TT 3 | at least 6 months after TT 2                       | 5 years                         |
| TT 4 | at least one year after TT 3 or during subsequent pregnancy | 10 years                       |
| TT 5 | at least one year after TT 4 or during subsequent pregnancy | All childbearing years          |

In the future, increasing numbers of women of childbearing age will have documentation of prior receipt of tetanus-toxoid-containing vaccines in early childhood or school-age. Other schemes of immunization can then be considered (Table 7). The rate of loss of immunity and the capacity to respond to a booster dose depend on the number of TT doses given (Fig 1), the age at immunization and the interval between the primary series and the booster dose. The duration of tetanus immunity following three doses of DPT given at one month intervals in early infancy is approximately 5 years, but the capacity to respond rapidly to a booster dose persists for much longer. Some studies suggest that a booster dose given as late as 30 years after primary immunization induces a strong and long lasting antibody response, although there is considerable variation between individuals (Simonsen et al 1986a). Other studies found a poor response to a booster dose given 15 years following a primary series (Collier et al. 1979). Since women who received only three doses of DPT in infancy may not respond well to one booster dose of TT, it is prudent to give them two doses of TT with an interval of one month, and complete the full immunization with one dose of TT one year later (or in a subsequent pregnancy). Women who can provide evidence of four doses of DPT in their childhood will need only one dose of TT at this contact (or in the current pregnancy) and one additional dose of TT one year later (or in the next pregnancy) (Table 7).
### Table 7: Guidelines for TT immunization of women who were immunized in the past

| Age at last TT immunization | Previous TT immunizations | Recommended immunizations at present contact/pregnancy | Later (at intervals of at least one year) |
|-----------------------------|---------------------------|--------------------------------------------------------|------------------------------------------|
| Infancy                     | 3 DPT                     | 2 TT*                                                  | 1 TT                                     |
| Childhood                   | 4 DPT                     | 1 TT                                                   | 1 TT                                     |
| School age                  | 3 DPT + 1DT/Td            | 1 TT                                                   | 1 TT                                     |
| School age                  | 4DPT + 1DT/Td             | 1 TT                                                   | none                                     |
| Adolescence                 | 4 DPT + 1DT at 4-6 yrs + 1TT/Td at 14-16 yrs | none                                                   | none                                     |

* At least 4 weeks between doses

Immunization of school children is another important approach (Schedules E and F, Figure 1). Children under age 7 years may be immunized with DT vaccine; older children should receive Td (or TT vaccine if Td is not available). In previously unimmunized schoolchildren, practical immunization schedules usually involve two primary doses given at school entry with at least a 4 week interval, a third dose administered at the next grade (after one year), and a fourth dose in the next grade.

**Figure 1: Expected duration of immunity after different immunization schedules**
The policy recommended by EPI is:

- All developing countries where women enter childbearing age without documentation of previous TT immunization in infancy or adolescence should adopt a five-dose TT programme (schedule G in Figure 1).

- Developing countries should progressively adopt schedule B (Figure 1) when they reach 80% coverage of the third dose of DPT in infants in all districts.

- Where possible, immunization of school children with TT or Td (schedules C-F in Figure 1) should be implemented.

A reduction in the number of doses of TT given to women of childbearing age should only be made when a high level of immunity in adolescent girls can be documented by immunization records or results of serological studies.
4. The expected effect of immunization on disease epidemiology

The epidemiology of vaccine-preventable diseases changes after immunization programmes are well established and high coverage is attained. The degree of change depends on the mechanism of action of the vaccine, the level of coverage achieved, the presence of non-human hosts for the organism, and characteristics of the infectious organism.

An important issue is whether vaccines protect against infection of humans by a bacteria or virus, or whether they only reduce the severity of disease among persons who are infected by the organism. Live viral vaccines such as measles and polio vaccines, for example, confer resistance to infection (and thereby prevent disease); this means that transmission of infection is also reduced by immunization. For these vaccines, the concept of "herd immunity" is relevant, that is the indirect action of the vaccine, once a high proportion of the community is immunized, on reducing transmission of the infectious agent and thereby making it less likely that persons (including unvaccinated persons) will be exposed to the agent.

Vaccines such as pertussis, however, appear to protect the individual against severe disease, but do not confer complete protection against infection and hence have less effect on transmission of the organism. BCG vaccine is thought to have very little effect on reducing transmission of TB because it confers such variable protection against pulmonary TB.

Toxoid vaccines such as TT confer antibodies against the toxin produced by certain organisms and hence protect against disease, but would not normally be expected to protect against infection by the organism. Interestingly, diphtheria toxoid immunization has resulted in a dramatic decline in both clinical disease and carriage rates. It is thought that the vaccine may reduce transmission because infected vaccinees are usually asymptomatic, and therefore they contribute less to airborne spread of the toxigenic organism than do unvaccinated infected individuals who have a membrane and cough. Pappenheimer's work on the molecular biology of diphtheria suggested that widespread immunization led to a decreased prevalence of the toxigenic strain of diphtheria, suggesting a mechanism for the "herd immunity" phenomenon (Pappenheimer et al 1983).

The presence of a non-human host or reservoir for the organism, such as monkeys for the forest pattern of yellow fever, means that immunization of humans may have little effect on transmission of the agent.
Vaccines that protect against infection have two major effects on the epidemiology of disease. These have perhaps been most extensively documented for measles but similar changes have also occurred with polioomyelitis and diphtheria:

- immunization changes the relative age distribution of cases, with a shift to older ages;
- outbreaks are likely to occur after some years of low incidence.

In addition, with all vaccines the following changes are likely:

- the proportion of cases of disease that occur in immunized individuals increases as coverage increases.
- antibody levels among immunized persons are often lower than among persons who acquired immunity through natural infection (an exception is tetanus immunization). This in turn will lead to lower levels of antibody transferred from mothers to their infants, with implications for the age at immunization of infants.

These main changes are discussed briefly below. There are of course other possible changes but those mentioned above have been of major programmatic importance for the EPI vaccines and are therefore discussed here.

**Changing age distribution of cases.** For vaccines that protect against infection and are administered in infancy, immunization of a large proportion of the community reduces transmission of the agent and reduces the chance of susceptible persons being exposed to the agent. Unimmunized children are therefore likely to reach an older age before they are exposed to the infectious agent, leading to an increase in the average age of infection. Though the proportion of cases in older children increases, the absolute number of such cases ultimately falls, due to the reduction in the overall incidence rate of the disease. The proportion of cases which occur among children below the recommended age for immunization may also increase, since this age group does not benefit directly from immunization. The number of cases will fall when very high coverage is reached, however. A shift in the age distribution of diphtheria has been seen in several developing countries recently, sometimes associated with a temporary increase in incidence in older age groups. In Yogyakarta, Indonesia, the incidence rate decreased markedly among children under five years of age after vaccine was introduced in 1977, but increased slightly in children aged 5-9 years from 1978-82 (Kim-Farley et al 1987).

The implications of changes in the age at infection depend on age-related changes in the outcome of infection. For measles, severity of disease is highest in children under 3 years of age. For rubella, which is a mild disease in children, the consequences of infection are much more serious in the childbearing years because of the risk of congenital rubella if a woman is infected during pregnancy. For poliovirus, the risk of paralysis increases with age at infection. Depending on the consequences of infection in older persons, countries may need to consider immunizing persons outside the primary target age group of the EPI once their programmes are well established (see section 5). For hepatitis B, infection during
early childhood is almost always asymptomatic but leads to development of the chronic carrier state in many infants. Conversely, adult infection is often symptomatic but is less likely to progress to chronic carriage of the virus.

**Outbreaks.** In recent years, many outbreaks of EPI diseases have been reported in countries that have well established immunization programmes, for several reasons. As discussed above, if immunization protects against infection, it slows the rate of accumulation of susceptibles so that there may be many years of low incidence followed by a large outbreak. Measles outbreaks were reported in 1988-9 in countries or areas with coverage between 64% and 85%, such as Harare, Zimbabwe (Kambarami et al. 1991), Muyinga health sector, Burundi, (Chen et al. 1994) and many Latin American and Caribbean countries, after several years of low incidence. These outbreaks may involve a large proportion of older children and adults, including unimmunized persons and immunized persons who did not respond to the vaccine or whose immunity waned. There have been a number of polio outbreaks in countries with relatively high immunization coverage (64% - 87%) with 3 or more doses of OPV in the routine immunization schedule (Deming et al. 1992, Kim-Farley et al. 1984, Otten et al. 1992, PAHO 1986, Schoub et al. 1992, Sutter et al. 1991). Low seroconversion rates to the primary series of three or four doses of OPV in hot climates appeared to contribute to some of these outbreaks.

Second, there may be pockets of low coverage, which are likely to occur in certain geographic areas, such as urban slums, remote rural areas or islands, or in certain population groups, such as ethnic and racial minorities (Hersh et al. 1991), nomadic peoples (Loutan et al. 1992), or persons with religious or philosophical objections to immunization (Novotny et al. 1988). Outbreaks in such pockets have been documented for measles and polio.

At the beginning of the 1990s there were several outbreaks of diphtheria. In industrialized countries, falling levels of immunity in adults has contributed to these outbreaks, perhaps because of reduced boosting of antibody levels from declining exposure to C. diphtheriae as circulation of the wild organism is reduced. However, other factors such as declining coverage among young children, and high population movement, have also been important in Russia, the Ukraine and some Newly Independent States of the former Soviet Union (EPI 1993h, 1994a, Galazka et al. 1995a). Outbreaks in developing countries such as Algeria, China, Ecuador, Jordan, Leshoto, Sudan and Yemen (Galazka et al. 1995b), highlight the need to maintain immunity against diphtheria in all populations, and to monitor the epidemiology of diphtheria in developing countries.

**Proportion of cases in immunized children.** As immunization coverage increases, a higher proportion of cases occurs among immunized children as illustrated in table 8. The closer to 100% is the coverage, the more likely it is that a case will be a "vaccine failure", i.e a child who was vaccinated but whom the vaccine failed to protect. Among all cases, then, as more are due to vaccine failure and fewer are due to non-immunization, the absolute number of cases decreases whilst the proportion of immunized cases increases.
Table 8: Illustration of changes in the proportion of cases which occur in immunized children at different levels, for a hypothetical population of 100 000 children

|                                                | Coverage 40% | Coverage 80% |
|------------------------------------------------|--------------|--------------|
| Total number of children                       | 100 000      | 100 000      |
| Number of unvaccinated children                | 60 000       | 20 000       |
| Number of cases in unvaccinated children       | 30 000       | 10 000       |
| Number of vaccinated children                  | 40 000       | 80 000       |
| Number of cases in vaccinated children         | 2 000        | 4 000        |
| Total number of cases                          | 32 000       | 14 000       |
| Proportion of total cases which are in vaccinated children | 6.3%         | 28.6%        |

Assumptions:
Disease incidence among unimmunized children: 50% per year
Disease incidence among immunized children: 5% per year

Antibody levels in immunized versus naturally infected adults. As discussed above, the lower antibody levels induced by immunization compared to natural infection have implications for the duration of immunity in immunized populations. As transmission of the agent decreases, antibody levels in immunized persons are less likely to be boosted by exposure to the agent, and immunity may be lost.

Another consequence of lower antibody levels in adults who were immunized as children, as compared to adults who were infected with the wild virus, is that mothers transfer less antibody to their infants, and infants therefore lose protective antibody sooner. For measles, for example, it may be possible to immunize children at an earlier age once most women of childbearing age have acquired immunity through immunization rather than disease. For most developing countries, this time has not yet arrived, since high measles immunization coverage has only been achieved relatively recently.

In tetanus, where infection with Cl. tetani does not induce immunity, the immunity level in a given age group depends only on immunization coverage. Thus, as TT immunization coverage increases in women of childbearing age, a higher proportion of neonates will have tetanus antitoxin. While this may reduce the response to the first and second doses of DPT, antibody levels after the third dose have been shown to be equal in infants whose mothers were or were not immunized against tetanus (Sangpetchsong et al. 1985).
5. **Additional schedules and strategies**

The main priority for the EPI has been to establish immunization programmes that can deliver the primary immunization series to over 90% of infants, and hence reduce the public health burden of the EPI diseases. The elimination of target diseases, however, will usually require supplementary activities that involve the administration of additional doses of vaccine. Additional doses may be given in a routine programme as boosters, where the main purpose is to increase the duration of protection from the different vaccines, especially in the absence of "natural" boosting from exposure to the infectious agent. Extra doses may also be given via special delivery strategies such as nationwide or localized campaigns, where the combination of the additional dose and the method of delivery is important to increase the immunogenicity of the vaccine (e.g. polio), to attempt to interrupt transmission of the agent by immunizing a large proportion of the population simultaneously (e.g. polio and measles), and/or to conduct "catch-up" immunization of older age groups who were missed as infants in the years when the coverage of the basic immunization programme was lower (e.g. measles). Lastly, special strategies may be needed to respond to outbreaks of the EPI diseases.

5.1 **Booster doses**

Until recently, the EPI has not addressed the issue of booster doses of EPI vaccines (EPI 1993e). The first priority has been to ensure that infants are completely immunized against target diseases at the youngest age possible. Where resources were limited, the EPI suggested that booster doses should not be considered until coverage levels for fully immunized infants was above 80% (EPI 1986).

Today, many countries have achieved coverage levels above 80% and are administering booster doses of various vaccines. The number and frequency of such booster doses depends on the epidemiological patterns of diseases in a particular country, the level of health services infrastructure, the ability to sustain high coverage of infants, and the availability of resources to buy vaccines.

**BCG.** There is much controversy over the effectiveness of repeated doses of BCG vaccine. Several European countries conduct routine tuberculin tests in immunized children and repeat BCG immunization in children until they develop a BCG scar and/or become tuberculin-positive. However, there is no evidence that the degree of protection from BCG is related to scar formation or to tuberculin conversion (Comstock 1971). On the other hand, there is evidence from some BCG trials that the protection afforded by BCG decreases with time after immunization, and some authors believe that repeating BCG immunization increases its efficacy (Kubit et al. 1983, Lugosi 1987), and revaccination is not associated with adverse events. The EPI recommends that research be conducted on the long-term effectiveness of BCG.
given in infancy, including the prevention of tuberculosis in adults who acquire HIV infection; the efficacy of different seed lot vaccines, and the safety and efficacy of BCG in HIV infected infants (EPI 1991a).

**DPT or DT vaccine.** Booster doses of DPT vaccine may be considered on the basis of maintaining immunity against each of the three component antigens of the vaccine.

**Table 9. Percentage of countries using different immunization schedules for DPT vaccine by WHO region (Galazka 1992)**

| Region             | Primary three doses in weeks (w) or months (m) of age | Booster doses |
|--------------------|------------------------------------------------------|---------------|
|                    | 6,10,14 w or 2,3,4 m                                  | 3-6 yrs       |
|                    | 3,4,5 m or 4,5,6 m                                    | 3-6 yrs       |
|                    | 2,4,6 m                                              | 3-6 yrs       |
|                    | 3, 5-6, 7-15 m                                        | 3-6 yrs       |
|                    | 12-24 m                                              | 3-6 yrs       |
| African            | 64                                                   | 31            |
| American           | 19                                                   | 33            |
| Eastern Mediterranean | 30                                              | 45            |
|                    | 25                                                   | 5             |
|                    | 30                                                   | 15            |
|                    | 57                                                   | 48            |
| Asian              | 57                                                   | 15            |
|                    | 18                                                   | 36            |
|                    | 63                                                   | 9             |
| W. Pacific**       | 23                                                   | 35            |
|                    | 35                                                   | 35            |
|                    | 23                                                   | 35            |
|                    | 16                                                   | 35            |

* No pertussis vaccine is used in Sweden. In Denmark, monovalent pertussis vaccine is used at 5 and 9 weeks and 10 months.

** In 5 countries, the DPT booster dose given at school entry is the fourth dose of DPT, since no dose is given one year after completing the primary series of DPT.

**Diphtheria component.** The duration of diphtheria immunity after a primary series of three diphtheria-toxoid-containing vaccines has varied widely in different studies. Studies in England and Italy showed that over 95% of children immunized with three doses of DPT or DT still had protective levels of diphtheria antibody 4-8 years later (Cellesi et al. 1989, Jones et al. 1989), and antitoxin levels were not related to the length of the interval between doses of DPT (Jones et al. 1989, Ramsay et al. 1991). Hence the UK does not administer a booster dose of DPT in the second year of life, but gives DT at school entry. However, studies in other countries have shown that antibody levels may fall below the "protective level" in a substantial proportion of children after the primary series, and also that immunity levels in schoolchildren appear to be lower in recent years (Crossley et al. 1979, Pichichero et al. 1987).

The duration of immunity against diphtheria may depend on the likelihood of exposure to diphtheria organisms (Simonsen et al. 1987, 1989) and thus may be different in developing countries than in developed countries. Data on persistence of immunity in developing countries are scarce, but recent outbreaks show that as immunization coverage increases, immunity gaps may arise in older age groups.
The appearance of diphtheria in older age groups in developing countries indicates the need to consider introduction of booster doses.

Routine use of booster doses of diphtheria toxoid in adults remains a controversial issue. Routine booster doses of Td vaccine are recommended every 10 years in many countries including Australia (National Health 1991), Canada (Health and Welfare 1984), Luxemburg and Switzerland (Bytchenko 1990), and the USA (ACIP 1991b, American Academy of Pediatrics 1991). Routine decennial booster doses of Td vaccine are difficult to monitor and usually this strategy is marginally effective. Td vaccine can be used instead of monovalent tetanus toxoid whenever tetanus toxoid is indicated e.g. in treating wounds in emergency rooms.

In many recent diphtheria outbreaks in Europe, adolescents and young adults were mainly affected. In Poland, additional routine booster doses of Td vaccine for adolescents at the age of 19 years have been introduced to prevent the spread of the diphtheria epidemic in young adults (EPI 1995). Serological investigations performed in several countries have shown a low level of diphtheria immunity among adults aged 20 to 50 years. A study in Denmark suggested that long-term protection against diphtheria may be assured by a booster dose of Td vaccine administered 20 years after the primary immunization (Simonsen et al. 1986b). The introduction of Td immunization of high risk groups in the adult population should be considered in industrialized countries. Td vaccine can be used in military service personnel and in other high-risk adults including medical service staff, kindergarten and creche personnel, teachers, students, alcohol and drug abusers and persons travelling to areas where diphtheria is endemic. In the face of a diphtheria epidemic, emergency immunization should involve mass immunization of affected age-groups or regions with high diphtheria incidence.

**Pertussis component.** The duration of immunity following pertussis immunization is also unresolved. Epidemiological investigations suggest that the efficacy of pertussis vaccine falls with time after immunization (Blennow et al. 1988, Jenkinson 1988). Serological studies show a steep decline of postvaccination antibody levels against various pertussis antigens (EPI 1993c) and one study suggested that the rate of decline may be more rapid after schedules with one month rather than longer intervals between doses (Booy et al. 1992). Antibody levels increase significantly after booster doses in the second year of life and/or at school entry, and may help to decrease pertussis infection during the school years. The pertussis component is not recommended after the age of school entry.

Recently, there have been several reports of pertussis in adults in industrialized countries. Decreased immunity among adults may be related to the reduced circulation of pertussis organisms in the community and less natural boosting. It has been suggested that acellular pertussis vaccines should be used to boost antibody levels in adults in an effort to reduce transmission of pertussis infection (Cherry 1992, 1993). This policy has not yet been evaluated, however.

**Tetanus component.** The expected duration of immunity against tetanus after the primary series of DPT is 5 years (see Fig 1). Administering additional doses in the second year of life and at school entry will prolong protection for at least 15 years,
and in the long term may be an important part of the overall strategy for neonatal tetanus elimination (see section 3.6).

**Current practice regarding DPT boosters.** Questions about the duration of immunity after a primary series of three doses of DPT are reflected by differences in the immunization schedules used in different countries. Figure 2 depicts schedules used in European countries and Table 9 shows DPT immunization schedules in six WHO regions. Some countries, mostly in the African and South East Asia Regions use only the primary series of three doses of DPT vaccine. Many countries recommend a booster dose of DPT vaccine one year after the primary series; upwards of 31% of countries in the African Region to 63% of countries in the European Region recommend a fourth dose of DPT vaccine at 12-24 months of age. Finally, in the USA and in about one third of countries in the American and Western Pacific Regions, an additional booster dose is administered at 4 to 6 years of age.

**Figure 2: DPT immunization schedules for European countries**

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The policy recommended by EPI is:

- In all countries, and particularly where pertussis is still an endemic disease and poses a serious health problem in infants and young children, the priority should be to reach at least 90% coverage with a primary series of three doses of DPT vaccine in infants in all districts.

- In countries where pertussis incidence has been considerably reduced by successful immunization programmes, a booster dose administered approximately one year after the primary series (at the middle or the end of the second year of life) is warranted. A booster dose of DPT will also help to maintain immunity against diphtheria, and will form part of the long-term strategy for neonatal tetanus control.

The need for additional booster doses of DPT or DT and their efficacy should be assessed by individual national programmes.

**Poliomyelitis vaccine.** The immunization schedule recommended by EPI calls for four doses of OPV given by 14 weeks of age. The importance of a birth dose of OPV has been discussed in section 3.1. If a dose of OPV is not given at birth, the fourth dose should be given at the time of the measles contact, or at any other contact with the health system in the first year of life. There should be an interval of at least 4 weeks between any two doses. The rationale for providing several doses of OPV is to assure initial seroconversion against all types of poliovirus, rather than to boost waning immunity.

In a number of countries where the circulation of wild polioviruses has been greatly reduced, if not eliminated, booster doses of OPV are commonly given at the second year of age and again before entering school.

**Measles vaccine.** Although measles can be controlled by achieving and sustaining coverage of over 90% of infants with a single dose, measles elimination is unlikely to be possible with the existing strategy. Recently measles epidemics have occurred in countries after prolonged periods of low disease incidence due to high immunization coverage (EPI 1989, EPI 1992e) - see section 4. Many countries have therefore introduced supplementary doses of measles vaccine. Industrialized countries that have low drop-out rates and high coverage through routine services have tended to adopt a routine two-dose schedule (Rosenthal and Clements 1992), but this has not been endorsed by WHO. On the other hand, countries in the Americas have adopted a mass campaign approach, as described in the next section. Drawing from this experience, WHO has adopted a policy of supplementary immunizations through mass campaigns (EPI 1994c).

Countries with a routine two-dose schedule usually administer the first dose between 12 - 15 months of age and the second dose between 6 and 12 years of age.
The second dose of vaccine is given to provide a second opportunity to immunize persons who were missed at the age for the first dose, and to immunize those who were immunized but failed to respond to the first dose (“primary vaccine failures”). Most persons who respond to measles immunization will have long-term or lifelong immunity, although studies have documented incidence of measles among persons who previously seroconverted after immunization (Mathias et al 1988, Reyes et al 1987). Revaccination of persons whose antibody levels have waned to low or undetectable levels appears to offer only transient benefit. In such persons, although antibody levels boost after revaccination, they subsequently fall to previous levels (Deseda-Tous et al 1978; Markowitz et al 1992). Therefore, decreasing the incidence of secondary vaccine failure is not a major objective of two-dose schedules.

It is not clear whether a two-dose schedule will improve measles control and more data on the cost-effectiveness and impact and of this strategy are needed. The challenge for most countries remains that of covering over 95% of each new birth cohort and administering the measles vaccine on time.

**Hepatitis B vaccine.** After the primary course of H B vaccine, surface antibody decays at a rate which is similar in all infants. Those who have high initial antibody levels will remain positive for antibody much longer than those who have a low post-vaccination antibody level. A significant proportion of immunized children have no detectable antibody 5 - 10 years following immunization, and subclinical infection, as demonstrated by detection of antibodies to HBV core antigen, has been reported. However, because such infections do not lead to clinical disease or to chronic carriage of HBsAg (Hall 1994), current thinking is that booster doses of H B vaccine are not needed (ACIP 1991a).

The longest follow-up of immunized children is still less than 15 years, however, and continuing study is important to assess the future need for booster immunization, particularly when persons immunized in infancy enter the sexually-active period of life (Hall 1993).

**Yellow fever vaccine.** The International Health Regulations require reimmunization at intervals of 10 years. Revaccination boosts antibody titre; however, evidence from several studies (Groot and Ribeiro 1962, Poland et al 1981; Rosenzweig et al 1963) suggests that yellow fever vaccine immunity persists for at least 30-35 years and probably for life.

### 5.2 Campaigns

Mass immunization campaigns are an integral part of the global polio eradication strategy, and are now recommended by WHO for use in measles elimination programmes (EPI 1994c, Global Programme for Vaccines 1994).

Polio eradication includes the following activities:

- The use of OPV in national and subnational immunization days aiming at the administration of two doses of OPV 4-8 weeks apart to all children under 5 years of age, regardless of their previous immunization status. Campaigns are
best conducted during the low season for polio transmission, which is usually the cool, dry season.

- "Mopping up" immunization activities
- In selected high risk areas conducted on a house-to-house basis. High-risk areas are those with polio cases at any time in the preceding 3 years, with low immunization coverage, or with epidemiologically defined risk factors such as urban slums. Two doses of OPV one month apart are administered to all children under age 5 years.
- Surveillance and investigation of cases of acute flaccid paralysis, followed by rapid outbreak response immunization where suspected cases are detected (see section 5.3).

Campaigns have also been used for measles elimination by countries in the American region and are being introduced in some countries of South-East Asia, combined with the polio eradication campaigns. The first phase of the elimination strategy is a mass campaign to immunize every child between the ages of 9 months and 15 years, irrespective of previous immunization or disease history (Anonymous 1994, Hospedales 1993). This strategy was based on the experience of Cuba, which had interrupted measles transmission by immunizing over 95 percent of children under age 15 years in 1988 (PAHO 1992). By the end of 1994, all countries in Latin America and the Caribbean will have implemented such campaigns. The short term impact of this strategy is dramatic, but in the longer term it is important to set up active measles surveillance to detect any suspected cases, which will trigger timely measles control measures. Additionally, high coverage of new birth cohorts must be achieved and maintained, and catch-up mass immunization in a narrower age range undertaken. Deciding on which age group to target for catch-up immunization will be dependent on the number of susceptibles who have accumulated in the respective age groups.

The policy recommended by EPI is:

Mass campaigns should be used in certain circumstances, especially in countries whose health infrastructure is inadequate to achieve high coverage through routine services. Such campaigns should be targeted to age groups identified through analysis of epidemiological data on age-specific attack rates of the disease. Urban areas, particularly those with low coverage and high measles incidence, may be operational targets in measles immunization campaigns. School-children or other age groups may be considered target groups in emergency diphtheria immunization campaigns in the face of diphtheria epidemics. Such campaigns should not be isolated events but should be part of a comprehensive, long-term strategy for polio eradication and measles control and elimination, and may include catch-up campaigns. Where possible, campaigns should include different EPI vaccines (EPI 1994c).
5.3 Outbreak response

Outbreak response immunization is localized mass immunization conducted rapidly in response to detection of an outbreak of an EPI disease.

The degree to which a country responds to an outbreak of measles is variable, and depends on: the availability of resources; the stage of development of the surveillance system; current measles coverage; measles incidence, and programme objectives. Countries with low measles vaccine coverage and high measles incidence should focus on developing and improving routine service. When an outbreak is observed, it is usually too late to intervene successfully. However, the opportunity should be taken to better understand why the outbreak occurred and to adjust strategies to reduce the chance of another outbreak occurring. In the event of an outbreak, countries may choose to increase access to case management services and to provide public information to increase knowledge about measles treatment and prevention through immunization. Sometimes political necessity overrides these criteria and alters the degree of response. An area experiencing a measles outbreak may be identified as high risk and subsequently be targeted for supplementary immunization activities.

Countries having high measles immunization coverage (e.g. 80% or more for at least three years), low incidence of disease, or both, may decide to provide a greater range of activities in the event of an outbreak. In addition to case management and public information, these include: supplementary immunization activities; case (or outbreak) investigation, i.e. the collection of information on the age, immunization status, date of onset of the rash, and other details about each case to use in analysing the cause of the outbreak, and intensive measles surveillance (an active searching by health workers for unreported or unexpected cases).

All countries should respond to outbreaks in refugee and other emergency relief settlements, with special emphasis on rapid supplementary immunization. Susceptible individuals should be immunized upon arrival at the settlement. If, despite this, a child in the settlement develops measles, all children between six months and five years of age should be immunized regardless of previous immunization history.

Transmission of measles in hospital must be prevented by immunization of all eligible children seen by health staff for any reason. An outbreak in a hospital setting should be responded to immediately with immunization of all in-patients aged between six months and fourteen years of age - they should be immunized regardless of previous immunization history.

A single case of diphtheria warrants a rapid and widespread immunization response covering affected age groups. Special attention should be given to close contacts of diphtheria cases; they should be monitored for signs/symptoms of diphtheria, bacteriologically tested for carriage of diphtheria organisms, and immunized against diphtheria. Previously immunized contacts should receive a booster dose of diphtheria-toxoid-containing vaccine, and a primary series should be initiated in
unimmunized contacts using DPT, DT or Td vaccines, depending on age. Useful guidelines on response to diphtheria outbreaks, including use of antibiotics, have been published (Benenson 1990, Farizo et al 1993, WHO 1994).

The detection of cases of polio should generate an outbreak immunization response with OPV. A single case of paralytic polio suggests a community with a low level of immunity. Even though many children will already be infected with the outbreak strain, others may be uninfected and the current recommendation is that if a case of suspected poliomyelitis is detected, one dose of OPV should be administered to all children less than 5 years of age living in the vicinity of a case, regardless of immunization status. The number of children, the distance, and the area to be targeted will depend on local resources and epidemiology (Hull et al 1994). Guidelines on the management of polio outbreak response activities have been published (EPI 1991c).
6. HIV infection and immunization

The recent epidemic of human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) has had a number of implications for immunization programmes. In some regions public confidence in immunization programmes has been undermined by concerns about cross-infection with HIV, while in other areas the safety and immunogenicity of immunization in HIV-infected individuals has been questioned.

If a sterile needle and syringe are used for every injection, as recommended by EPI, there is no risk of transmitting HIV or any other blood-borne infection through immunization. There is no evidence that immunization programmes have contributed to the spread of HIV infection.

Since the mid-1980s EPI and the Global Programme on AIDS have supported and monitored studies on immunization in HIV-infected individuals, particularly children. Recommendations for immunization in the presence of HIV infection are based on the severity of EPI target diseases in HIV-infected individuals, the immunogenicity and safety of vaccines in these individuals and the stage of HIV infection.

6.1 EPI target diseases in HIV-infected individuals

Measles and tuberculosis are more severe in HIV-infected than in seronegative individuals. Measles tends to occur earlier in life (Embree et al. 1989) and has a high mortality rate in HIV-positive children (Kaplan et al. 1992, Krasinsky & Borkovsky 1989). Primary tuberculosis infection is more likely to be associated with progressive disease in HIV-infected than in seronegative individuals. Reactivation of disease in adults is also more likely: while the lifetime risk of reactivation of tuberculosis is 10% overall in seronegative persons, it rises to 8-10% per year among HIV-infected persons. The response to treatment is lower in HIV-infected individuals, and the mortality rate is higher (Nunn 1991). The HIV epidemic is leading to a dramatic increase in the global number of tuberculosis cases (Nunn et al. 1990, Schulzer et al. 1992). Information on the incidence and severity of the other EPI target diseases in HIV-infected individuals is limited.

6.2 The safety of EPI-recommended vaccines in HIV-infected individuals

As HIV-infection results in a progressive 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 has been no reported increase of adverse reactions in HIV-infected persons to the live vaccines OPV and measles,
nor to DPT and hepatitis B vaccines, which contain no live organisms (Clements et al., 1987, LePage et al., 1992, McLaughlin et al., 1988, Onorato et al., 1988, Ryder et al., 1993). Concern has been expressed that simultaneous administration of multiple antigens (even inactivated vaccines) might theoretically accelerate the disease process. Clinical and laboratory data do not support this (Onorato & Markowitz, 1992).

Isolated cases of disseminated BCG disease (generalized infection due to BCG) have been reported among infants with asymptomatic HIV infection (Blanche et al., 1986, CDC, 1985, Houde et al., 1988, Micelli, according to ten Dam, 1990b, Ninane et al., 1988, Vilmer et al., 1984). However, prospective studies comparing BCG immunization in HIV-infected and uninfected infants have failed to show any difference in the risk of local or regional complications (Laemant-LeCoeur et al., 1991, Ryder et al., 1993). There have, however, been reports of severe reactions in adults with symptomatic AIDS who received BCG vaccine (CDC, 1985, Reynes et al., 1989). There is a concern that OPV could be associated with an increased risk of paralytic polio in contacts, since many parents of HIV-infected infants are themselves infected with HIV. In countries such as the USA where many adults lack immunity to poliomyelitis because wild virus circulation has ceased, there may be a theoretical advantage in administering killed polio vaccine (ACIP, 1994). However, in developing countries, adults have naturally-acquired immunity and the risk of paralysis in contacts is likely to be very low.

### 6.3 The immunogenicity of EPI-recommended vaccines in HIV-infected individuals

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 (Borkovsky et al., 1992). Studies of the immunogenicity of EPI-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. In a study in Zaire, a similarly high proportion of children with perinatally acquired HIV infection and children without HIV infection acquired protective antibody levels to tetanus and poliovirus types 1, 2 and 3, but the response to diphtheria was lower (71%) in HIV-infected children than in uninfected children (99%) (Ryder et al., 1993). The response to measles vaccine is also lower in HIV-infected than non-infected infants (Cutts et al., 1993, Oxtoby et al., 1988), and is related to severity of infection. In a study in Zaire, among HIV-uninfected, asymptomatic HIV-infected, and symptomatic HIV-infected children, 89%, 77% and 36% respectively seroconverted after Schwarz vaccine at age 9 months (Oxtoby et al., 1988). Antibody levels induced by the EPI vaccines tend to be lower in HIV-infected individuals and to fall more rapidly over time than in non-infected persons (Onorato et al., 1988, Ryder et al., 1993). However, HIV-infected women have been shown to develop levels of tetanus antibody after two doses of vaccine during pregnancy similar to those of seronegative women (Baende et al., quoted in Onorato and Markowitz, 1992).

Several studies have demonstrated an impaired response to HB vaccine in HIV-infected adults, who have lower seroconversion rates to the primary series of 3
doses of HB vaccine and more rapid loss of antibody to surface antigen than individuals not infected with HIV (Geseman et al., 1988). Nonetheless, HIV-infected persons who respond to vaccine appear to be protected against serious illness and against chronic surface antigen carriage. Study of the response to HB vaccine in HIV-infected infants is needed.

6.4 Current WHO/UNICEF recommendations for the immunization of HIV-infected individuals

In collaboration with UNICEF, WHO has established guidelines for the immunization of children and women of childbearing age with EPI-recommended vaccines (EPI 1987a, EPI 1987b, CDC 1992, SPA/EPI 1987, GPA/EPI 1989) (Table 10). It is recommended that individuals with known or suspected asymptomatic HIV infection receive all EPI vaccines as early in life as possible, according to the nationally recommended schedules. Because of the risk of early and severe measles infection, these infants should receive a dose of standard measles vaccine at 6 months of age with a second dose as soon after age 9 months as possible (GPA/EPI 1989). Individuals with symptomatic HIV infection can receive all the EPI vaccines except BCG and yellow fever vaccines.

Table 10: World Health Organization/UNICEF recommendations for the immunization of HIV-infected children and women of childbearing age

| Vaccine       | Asymptomatic HIV infection | Symptomatic HIV infection | Optimal timing of immunization |
|---------------|----------------------------|---------------------------|-------------------------------|
| BCG           | yes                        | no                        | birth                         |
| DPT           | yes                        | yes                       | 6, 10, 14 weeks               |
| OPV*          | yes                        | yes                       | 0, 6, 10, 14 weeks            |
| Measles       | yes                        | yes                       | 6 and 9 months                |
| Hepatitis B   | yes                        | yes                       | As for uninfected children    |
| Yellow fever  | yes                        | no**                      |                               |
| Tetanus toxoid| yes                        | yes                       | 5 doses***                    |

* IPV can be used as an alternative for children with symptomatic HIV infection  
** Pending further studies  
*** 5 doses of tetanus toxoid for women of childbearing age as for non-HIV infected persons

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.
Children with known or suspected HIV infection are at increased risk of severe measles. Such children should be offered measles vaccine as early as possible. Standard WHO recommendations for children at high risk of contracting measles are to immunize with measles vaccine at 6 months of age with a second dose at 9 months. Children with known or suspected HIV infection should be considered to be in this high-risk category and receive measles vaccine at 6 months of age, followed by a second dose at 9 months (GPA/EPI 1989).
7. Reactions following immunization

Although modern vaccines are extremely safe, some vaccines may lead to reactions. The occurrence of an adverse event after the administration of a vaccine, however, does not prove that the vaccine caused the symptoms. An association between an adverse event and a specific vaccine is suggested:

- if there is an unusual clustering of a condition in vaccinees in a limited interval after immunization, or

- if vaccinees experience the event at a rate significantly higher than that in groups of similar age or background who have not recently received a vaccine.

Adverse reactions may be caused by faults of administration (programmatic errors) or be associated with the properties of vaccines.

7.1 Programmatic errors

The most common adverse events caused by programmatic errors are abscesses following inadvertent inoculation into the superficial layer of the skin of poorly mixed adsorbed vaccines (sterile abscesses), and abscesses that arise because needles and syringes are not sterilized properly. Serious adverse events may arise if vaccines are given to persons for whom they are truly contraindicated, for example BCG and measles vaccines can cause disseminated disease in immunosuppressed individuals.

7.2 Reactions related to inherent properties of vaccines

Adverse events may be caused by reactions to the immunizing antigen itself or to other components of the vaccine, such as antibiotics (kanamycin or neomycin in measles vaccine, streptomycin or neomycin in OPV), a preservative (merthiolate, a mercury-containing compound present in DPT, DT and TT) or aluminium adjuvant present in adsorbed vaccines.

Adverse events range from mild (for example, a transient fever or local irritation following DPT vaccine) to serious (e.g. vaccine-related paralysis following OPV immunization). Mild local reactions following DPT vaccine are quite frequent and occur in 20% - 50% of vaccinees. Rarely occurring sterile abscesses have been reported following immunization with vaccines containing an increased amount of aluminium adjuvants (Bernier 1981). Fever and rash after administration of measles vaccine and tenderness, redness and swelling after typhoid or cholera immunization are other examples of mild adverse reactions following immunization.
Localized and regional adenitis and prolonged ulceration resulting from BCG immunization may be related to the strain of BCG bacilli in the vaccine and often occur after a change in the source of vaccine used in a country. Some substrains of BCG appear to be more likely to cause adenitis than other substrains. Axillary or cervical lymphadenitis usually heals spontaneously and it is best not to treat the lesion if it remains unadherent to the skin. An adherent or fistulated lymph gland, however, may be drained and an anti-TB drug may be instilled locally. Some authors recommend systemic treatment of severe persistent lesions with erythromycin (Bhandari et al. 1980), while others have tried systemic treatment with isoniazid (Hanley et al. 1985). However, lesions have persisted despite one month of therapy with either drug, and placebo-controlled trials of treatment are needed (Hanley et al. 1985). BCG infection that may occur in immunosuppressed individuals should be treated with anti-tuberculous drugs (Romanus et al. 1993).

Some persons, especially in older age groups, may have a hyperimmune reaction to diphtheria toxoid, or more rarely tetanus toxoid, after receiving booster doses of those vaccines when they have high titres of the respective antitoxin. Some live virus vaccines prepared on hen's egg tissues, such as yellow fever or influenza vaccines, may have a potential risk for egg-sensitive individuals. However, only a few reactions are clearly associated with specific hypersensitivity.

Severe reactions are extremely rare. Major reactions include encephalitis after mumps and measles vaccines, encephalopathy after pertussis vaccines, and paralysis after oral polio vaccine among recipients of the vaccine or their contacts. The risk of OPV-related paralysis has been estimated through passive surveillance in the USA, where about one case has occurred per 2.5 million doses of OPV distributed during 1980-1989 (Strebel et al. 1992). Many adverse events have been reported as related in time to DPT immunization. However, a comprehensive analysis of the relationship between various events and immunization against pertussis did not indicate a causal relationship between DPT immunization and infantile spasms, Reye's syndrome, or sudden infant death syndrome. There is insufficient evidence to indicate the presence (or absence) of a causal relation between pertussis immunization and aseptic meningitis, chronic neurological damage, Guillain-Barre syndrome, haemolytic anaemia and other conditions (Howson and Fineberg 1992a). On very rare occasions, DPT immunization may cause acute encephalopathy, convulsions, or shock-like state or hypotonic and hyporesponsive episodes (Cody et al. 1981, Howson and Finberg 1992b).

Although the rates of serious events are difficult to estimate precisely, they are far less frequent than the complications caused by the disease themselves (Table 11).
Table 11. Estimated rates of adverse events following DPT and measles immunizations per 100 000 injections compared to complication rates of natural pertussis and measles per 100 000 cases.- According to Galazka et al. (1984)

| Condition           | Pertussis disease | DPT immunization | Measles disease | Measles immunization |
|---------------------|-------------------|------------------|-----------------|---------------------|
| Encephalopathy/encephalitis | 90-4000          | 0.2              | 50-400          | 0.1                 |
| Convulsions         | 600-8000          | 0.3 - 90        | 500-1000        | 0.02-190            |
| Death               | 100-4000          | 0.2              | 10-10000        | 0.02-0.3            |

The detection of serious adverse events following immunization is important for the success of a programme, since such events can influence community acceptance of immunization. In developing countries, the majority of complications recognized following immunization appear to be programme related; thus the underlying causes of these cases need to be identified and corrected.

The policy recommended by EPI is:

- All immunization programmes should monitor adverse events following immunization. A field guide for surveillance of adverse events has been produced (EPI 1993f). Each adverse event should be investigated and efforts should be made to determine its cause. The detection of adverse events should be followed by appropriate treatment and communication with parents, health workers, and if several persons are affected, with the community. If the adverse event was determined to be due to programme errors, operational problems must be solved, by appropriate logistical support, training and supervision.
8. Other vaccines that can be used as a part of EPI

There are several other vaccines available which are used in different countries but are not yet recommended for use worldwide by the EPI. Some vaccines, such as Japanese encephalitis and Pig bel vaccines, are against diseases which are prevalent only in limited geographical areas; others such as H. influenzae type b (Hib) vaccine are used in industrialized countries but data on their cost-effectiveness in developing countries are not yet available; others such as pneumococcal vaccines are effective in adults but preparations for use in infants under 2 years of age have not yet been developed. This section provides a summary of information on vaccines currently available that certain countries may choose to include in their immunization programmes, and references to useful review papers. Factors that affect the decision to incorporate a new vaccine into a national vaccination schedule are summarized in Table 12.
Table 12. Factors affecting inclusion of a vaccine in a national programme (EPI 1993g)

| Priority of the disease | Morbidity and mortality from the disease  
| | Age-specific attack rates  
| | Availability of other interventions for its control  
| Characteristics of the vaccine | Immunogenicity  
| | Efficacy  
| | Duration of immunity  
| | Interaction with other antigens  
| | Safety/adverse reactions  
| | Dose  
| | Route of administration  
| | Storage  
| | Thermostability  
| | Potential for combination with other antigens  
| Programmatic feasibility | Ability to reach the target population before the age of maximum risk  
| | Potential contact points with target population (health services, schools etc)  
| | Cost of alternative strategies  
| Vaccine supply | Global production adequate?  
| | Technology transfer to developing countries possible?  
| | Affordability  

8.1 Rubella vaccine

In childhood, rubella is a mild infectious disease in both industrialized and developing countries. The public health importance of the disease relates to congenital rubella syndrome (CRS) (EPI 1991d, EPI 1992f, Galazka 1991). When maternal rubella infection occurs during the first 3 months of pregnancy, foetal infection results in 90% of cases, with severe permanent consequences including blindness, deafness, and congenital heart defects. Spontaneous abortions and stillbirths are common. In the absence of immunization, rubella is endemic, and most children acquire the infection before they reach childbearing age. The proportion of women of childbearing age that are susceptible to rubella varies widely between and within regions, and there are few data on the incidence of CRS in developing countries.

Most industrialized countries include rubella vaccine in their national immunization programmes, most commonly as a combined measles-mumps-rubella (MMR) vaccine which is administered instead of single antigen measles vaccine in the second year of life. Some countries give a second dose at school age. Other countries conduct selective immunization of adolescent female children with single antigen rubella vaccine. Universal rubella immunization has not been recommended by
WHO to date, because of the need for very high coverage to avoid the potential for an increase in the risk of CRS in the presence of an immunization programme. As discussed in section 4, immunization acts to increase the average age at infection, and if coverage is not high enough to reduce rubella transmission close to zero, there could thus be a paradoxical increase in CRS incidence in the presence of an immunization programme. The cost of MMR vaccine is also approximately twice that of single antigen measles vaccine. Now that many developing countries are sustaining coverage of measles vaccine above 85%, there is a need for research on the burden of CRS in developing countries and for cost-benefit analysis of rubella immunization.

8.2 Japanese encephalitis vaccine

Japanese B encephalitis (JE) is caused by an arthropod-borne virus (arbovirus). JE occurs in Southeast Asia and the Western Pacific countries (ACIP 1993a; EPI 1994b; Igarashi 1992). It is estimated that 2.4 billion persons are at risk and 20,000 cases occur each year with a case fatality rate of 25% and residual disease in about 30% of the survivors. In areas where JE is endemic, the annual incidence ranges from 1 - 10 per 10,000. Children younger than 15 years of age are mainly affected.

At present, two types of formalin-inactivated JE vaccine are in use, one derived from mouse brain and the other from primary hamster tissue culture. The vaccine produced in mouse brain is purified to remove myelin basic protein and is not associated with central nervous system damage in recipients. For primary immunization two doses of mouse brain JE vaccine are administered subcutaneously at an interval of 1 - 2 weeks. One additional dose is recommended a month after the primary immunization. A booster dose is recommended every 1 to 4 years. The vaccine has been shown to be highly effective and safe. The vaccine is produced in Japan, Republic of Korea, Taiwan, Thailand, and Vietnam. Purified JE vaccine is also produced and used in India (Rao Bhau 1992). An inactivated JE vaccine produced in baby hamster kidney cell culture was developed in China. It has been used since 1967 on a massive scale among children between 1 and 10 years of age in China.

Given the severity of the disease, particularly in young children, and the effectiveness of the available inactivated vaccines, countries where JE is endemic should consider its inclusion in their immunization programmes. There are no data on whether JE vaccine can be given simultaneously with measles or other EPI vaccines.

Issues that need to be resolved in further studies include: (1) the earliest age for immunization; (2) the need for booster doses; (3) whether JE vaccine can be given simultaneously with other EPI antigens, and (4) ways to decrease the cost of JE vaccine.

8.3 Meningococcal vaccine

Neisseria meningitidis causes both endemic and epidemic disease, principally meningitis and meningococcaemia (Wright 1989). Case fatality ratios reach 10-20% despite treatment in industrialized countries, and may be higher in developing
countries. Most meningococcal diseases are caused by meningococci of serogroups A, B and C. Serogroup A is mostly responsible for large epidemics. Meningococcal disease is an important epidemic and endemic cause of morbidity and mortality, particularly in the sub-Saharan meningitis belt of Africa. In epidemics, attack rates are higher than 500 cases per 100 000 population and about half of all cases are reported in children aged 0-4 years.

Safe and effective vaccines composed of monovalent groups A and C, bivalent A + C or quadrivalent A,C, W-135 and Y capsular polysaccharides are currently in use. A single dose of group A polysaccharide given to persons over 2 years of age will protect for 1 to 3 years. For children less than 2 years of age, two doses of group A polysaccharide vaccine are required 3 months apart to achieve protective levels of immunity. The vaccine has a clinical efficacy of 85-95% against serogroup A disease and is of use in controlling epidemics. Group C polysaccharide vaccine is effective in adults, but fails to elicit protective levels of antibodies in children less than two years of age. The linkage of a carrier protein to the polysaccharide (conjugate vaccine) allows the polysaccharide (PS) to provide long lasting immunity. Progress in development of conjugate PS-protein vaccines for invasive H. aemophilus influenzae type b disease suggested that the same approach could be taken to prepare meningococcal A/C conjugate vaccines. Progress is ongoing to reach this goal.

Serogroup B is responsible for approximately 50% of endemic meningococcal infections in developed countries, but the group B polysaccharide is a poor antigen. Because some of the molecular structure is identical between meningococcal B polysaccharide and human brain tissue, safety concerns were raised on this cross-reactivity and a new approach has been taken using outer membrane protein (OMP) as potential candidate vaccine. OMP based vaccines have been developed in Norway (protective efficacy, PE, 57%) and in Cuba (PE in Cuba 80%, in Brazil 74% in infants 4 years old, 47% in children between 2 and 4 years of age, and no protection in children less than 2 years of age).

Currently available meningococcal polysaccharide vaccine is not recommended for routine infant immunization because of the short duration of immunity and the failure to protect against endemic serogroup B infections. However, widespread emergency immunization can control meningococcal A/C disease if implemented early in the course of an epidemic. Therefore, an effective meningitis surveillance is needed to detect the emergence of an epidemic in order to institute immunization at the earliest possible time. Studies in Burkina Faso showed that meningitis incidence rate of 15 per 100 000 averaged over 2 weeks is a specific and predictive threshold for an epidemic and for initiating emergency immunization (Moore et al. 1990, 1992).

**8.4  H. aemophilus influenzae type b vaccine**

H. influenzae type b (Hib) is a common cause of bacterial meningitis and a variety of serious and potentially life-threatening infections, including pneumonia, epiglottitis and sepsis in infants and older children (ACIP 1993b; Pediatrics, supplement 1990; Wright 1989). A polysaccharide vaccine has been available for several years but was not immunogenic in infants. Recently, however, safe and effective conjugated Hib
vaccines have been developed and licensed for use in several industrialized countries, where they have dramatically reduced the incidence of Hib meningitis. They contain Hib polysaccharide conjugated to diphtheria or tetanus toxoid, to a CRM197 mutant C. diphtheriae toxin protein, or to an outer-membrane protein complex of Neisseria meningitidis group B. Vaccines are given in a schedule of three doses in infancy (together with DPT), with (eg USA) or without (eg UK) a booster dose at age 12-18 months. A combination DPT-Hib conjugate vaccine is now available (ACIP 1993b). It would be premature to recommend the wide-scale use of conjugated Hib vaccine in developing countries until cost-effectiveness of such immunization is known. However, the high case fatality rate due to Hib meningitis and H. influenzae-pneumonia in developing countries warrants thorough testing of the efficacy of conjugated Hib vaccines given in infancy, and a large efficacy study is in progress in the Gambia.

8.5 Pneumococcal vaccines

Streptococcus pneumoniae is responsible for three types of disease, pneumonia, otitis and meningitis. It is the leading cause of severe pneumonia in children under 5 years of age, causing over 1 million deaths each year. The current vaccine against S.pneumoniae is composed of capsular antigens to 7, 9 or 23 serotypes, which cause 60% to 90% of the infections in humans, and is immunogenic in persons over 2 years of age (Shann 1990). In some countries, recommendations are to give a dose of vaccine to children over 2 years old who are at high risk (those with sickle cell disease, chronic renal failure, immunosuppression from organ transplantation, leaks of cerebrospinal fluid, and HIV infection) (Feldman 1991), and countries such as the USA also include all persons 65 years of age and older in the target group.

It is difficult to prepare an effective vaccine against S. pneumoniae because protection is serotype specific and there are many (up to 80) different serotypes. Furthermore, like other pure polysaccharide vaccines, pneumococcal vaccine is poorly immunogenic in children, and is not recommended for infant immunization programmes. However, the development of a pneumococcal vaccine effective in infants is a high priority, and efficacy trials of pneumococcal conjugate vaccines will soon be conducted in developing countries. In children the immune response to the 6 serotypes involved in most of the infection, appeared over 4 years of age, and the PS candidate vaccines are unlikely to provide protection for more than 60-70% of invasive disease. An alternative approach has been taken using other components of the bacteria like pneumococcal surface protein (PspA), pneumolysin or protein 37K.D.

8.6 Pig bel vaccine

Pig bel is a severe form of food poisoning; it is a necrotizing inflammatory disease of the small bowel (necrotizing enteritis) caused by toxins elaborated by Clostridium perfringens (welchi) type C. This disease is an endemic and an important cause of morbidity and mortality in children in Papua New Guinea. A condition with similar etiology has been reported from the south of China (Shann et al. 1979) and from a refugee camp on the Thai-Cambodian border (Karanth et al. 1986).
A toxoid prepared from Clostridium welchi type C is available and appears to be effective in children aged 1 to 15 years (Lawrence et al. 1979, Murrell 1982) and in infants, when it can be given simultaneously with DPT vaccine (Davis & Walker 1982). Routine immunization of children with Cl. perfringens toxoid was introduced in Papua New Guinea in 1980 in the five highland provinces and since then the incidence of the disease has fallen dramatically. Three intramuscular injections are given at two-monthly intervals to infants, at 2, 4 and 6 months of age, simultaneously with DPT immunization. Protection lasts for 2 to 4 years.

8.7 Typhoid vaccine

Typhoid fever remains an important and underestimated disease in many regions of the world (causing 560,000 deaths every year globally) and it poses a risk for travellers. In most endemic areas the incidence of typhoid fever is highest in children 5 - 19 years of age; hence a vaccine is needed that can establish durable immunity prior to school age (Levine 1990, Levine et al. 1991, Editorial 1992, Ivanoff et al. 1994).

Existing inactivated, injectable typhoid vaccines prepared from whole cell organisms confer protection after two doses in 51 - 88% of school children, but cause high rates of adverse reactions. The efficacy of killed vaccine has never been shown in controlled trials in children less than 2 years of age.

Live oral typhoid vaccine contains an attenuated strain of Salmonella typhi, Ty21a. The vaccine is safe and its efficacy has been evaluated in field trials in endemic areas. The level of protection is influenced by the formulation of the vaccine, the number of doses given, and the immunization schedule used (Levine 1990). With a liquid formulation, a 67% protective efficacy has been obtained after 7 years of follow up in an endemic area.

Purified Vi antigen, a polysaccharide capsule in the surface of S. typhi, has been used as a one-dose injectable vaccine in Nepal and South Africa, where the vaccine provided, respectively, 72% protection at 17 months, 64% protection at 21 months and 55% protection after 5 years of follow-up.

Both Ty21a and Vi polysaccharide are currently licensed and available, and offer an alternative to the poorly tolerated whole cell typhoid vaccine (Levine 1990). There is, however, insufficient information on the efficacy of these vaccines in children below 2 years to recommend them for use in infant immunization programmes at this time. Because of the current increased resistance against antibiotics, immunization should be considered as an alternative strategy in combatting typhoid fever.

8.8 Cholera vaccine

Cholera is estimated to cause more than 150,000 deaths each year in developing countries (WHO 1991). About one-third of the deaths are in children under 5 years of age, one-quarter in children age 5 - 14 years, and the remainder in adults. Parenteral immunization with the killed whole-cell vaccine is of no practical value in epidemic control or management of contacts of cases. This vaccine provides only partial protection (50%) of short duration (3 - 6 months), and is not regarded as a
useful public health intervention. Attention has instead turned to the development of oral vaccines that could more efficiently stimulate local immunity (Clemens et al. 1990).

Both inactivated and live oral cholera vaccines have been developed (Levine and Kaper 1993). Two oral inactivated vaccines were evaluated in Bangladesh in the mid-1980’s and three doses provided 68% protection for at least three years in persons above 5 years of age. However, certain limitations were noted: the level of protection was markedly lower and lasted for only 6 months in children less than 5 years of age, and the vaccines provided less protection against the El Tor biotype than the classical biotype, after three years of follow-up. A trial conducted in Peruvian adults showed an 86% protection against El Tor after 6 months of follow-up. Most of those vaccinated were of blood group O.

Significant progress has been made recently towards the development of a one dose live attenuated cholera vaccine, containing the strain CVD-103 HgR, a V. cholerae 01 mutant strain, in which genes encoding cholera toxin have been deleted. In adult volunteers and children over 5 years of age the vaccine is immunogenic. Efficacy studies are now underway in children below 2 years of age. A practical and effective vaccine that can be used in all children is still needed.

New oral one-dose live candidate vaccines against El Tor biotype are under investigation. First results in US volunteers are encouraging (protective efficacy 83%). In March 1993, groups from Calcutta and Dhaka reported an apparently major outbreak of a cholera-like illness caused by a serotypically novel strain of Vibrio cholerae. This strain, which did not react with antisera for any of the 138 recognized serotypes of V. cholerae, has been designated V.cholerae 0139 Bengal. New oral killed and live candidate vaccines against cholera 0139 are under evaluation, as well as combined vaccines (01 and 0139).

8.9 Other vaccines under development

There is an urgent need for development of new vaccines. No successful vaccine against any human parasite has yet been developed. Malaria remains an important public health problem and an effective, safe and cheap vaccine would be a decisive factor in controlling malaria. One vaccine called "SPf66", a chemically synthesized vaccine, underwent efficacy tests in Africa, having demonstrated immunogenicity in Colombia and Tanzania (WHO 1994). SPf66 is a safe and highly immunogenic vaccine and reduces disease incidence by 31% in Tanzania (Alonso et al. 1994) and 60% in Ecuador (Sempertegui et al. 1994). While these figures fall far short of the 80% and more efficacy of EPI vaccines, malaria's high death toll means that even a partially effective vaccine could be a valuable weapon. These preliminary results provided a basis for attempts to improve the efficacy of malaria vaccine.

A modern plague - the pandemic caused by HIV - is recognized to be an international health problem of extraordinary scope and unprecedented urgency. A safe and effective vaccine to prevent the acquisition of HIV or to delay or prevent progression of HIV disease in those already infected, would be a vital addition to global AIDS prevention and control efforts. Although considerable progress in the development of HIV vaccines has been made, formidable obstacles remain. Animal
models used to test HIV vaccines have several limitations; the genetic diversity of 
HIV may require an effective vaccine to be based on many viral strains; the immune 
correlates of protection remain unknown. Notwithstanding their marked genetic 
variability, the envelope glycoproteins of HIV, gp120 and gp160, have long been 
the primary foci for vaccine development. However, the degree to which the 
vaccines might confer protection against homologous or heterologous strains of 
HIV, or induce cell-mediated cytotoxicity, has remained uncertain.

Infections of the respiratory tract, such as those caused by respiratory syncytial and 
para-influenza viruses, are another great scourge; vaccines against these infections 
are under development.

In developing countries, those most at risk of enteric infections and diarrhoeal 
diseases are infants and young children. If safe, practical and effective vaccines 
extisted against rotaviruses, shigellae, and enterotoxigenic E.coli, the disease burden 
from enteric infections could be greatly reduced.

The pace of vaccine research and development has quickened with better 
understanding of the antigens responsible for disease and protection, and with the 
avdent of powerful molecular and cell biological techniques. We are now - as was 
noted at the first Bellagio Conference - "on the threshold of another major 
revolution in vaccine research, comparable or even exceeding in its scope the era 
that began when poliomyelitis virus was first grown in tissue culture" (Nossal 
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