REVIEW ARTICLE

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An Update on the Global Programme for Vaccines and Immunization

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Since 1986, the immunization programmes throughout the world have changed their focus to the control or elimination of major childhood diseases, and new vaccines have become available, while yet others are being developed. 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 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 article provides a review of present immunization policies.

THE TARGET DISEASES

Tuberculosis, caused by *Mycobacterium tuberculosis*, caused an estimated 2.6 million deaths worldwide in 1990[1]. The pandemic of HIV infection and an increase in multi-drug-resistant tuberculosis bacteria have profoundly worsened the public health burden of tuberculosis[1]. Diphtheria is a bacterial infection caused by *Corynebacterium diphtheriae*, transmitted from person to person through close physical and respiratory contact. Like other respiratory infections, the transmission of diphtherial infection in the overcrowded and poor socio-economic conditions has increased to a great extent. 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[2]. 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 Ukraine.

Tetanus is caused by the action of potent neurotoxin produced during the growth of the anaerobic bacteria, *Clostridium tetani*, in necrosed tissues such as in the 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 elderly persons, as 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 to tetanus.

Pertussis (whooping cough) is a bacterial respiratory infection caused by *Bordetella 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 the disease may manifest

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with spells of apnea. Many of the symptoms are thought to be caused by the toxins released by *B. pertussis*, in particular 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 vaccine[3-5].

Poliomyelitis is an acute viral infection spread via the fecal-oral route, thus transmission is higher in areas of poor sanitation. Where sanitation is good, pharyngeal spread becomes more important. The majority of wild polioviral infections are asymptomatic; the risk of paralysis is approximately 1 in 200 infections among infants <1 y old, and 1 in 100 infections among the children aged 1-14 y. Factors increasing the likelihood of paralysis include the administration of tonsillectomy during the incubation period of 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[6]. 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.

Acute 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 a 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). 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 diseases and liver cancer, which arise in carriers of the HBV virus, who are identifiable through detection of HBsAg. The younger is the age at the time of infection, the higher are the chances 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 play 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[7]). Table 1 summarizes the information on the target diseases, which is most relevant to the design of control programmes.

AVAILABLE VACCINE PREPARATIONS

Bacterial vaccines include *Bacille Calmette Guerin* (BCG) that contains live attenuated *Mycobacterium 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 vaccines, all of which are 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.

BCG:

Although BCG is the most widely used vaccine in the world (85% of the 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/Chengalput, to approximately 80% in the UK[8]. There is no consensus on the reasons for this variation. Efficacy does not depend on BCG strain or manufacturer[9]. 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 neither been correlated with the degree of tuberculin test sensitivity induced by the immunization, nor with BCG scar size. Data showing that BCG protects against tuberculosis meningitis and against military tuberculosis (estimated 75-86% protection[10]) 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[11]. 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 the antigenicity. 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[12,13]. Diphtheria outbreaks in adults in Europe show the need to maintain immunity against the disease throughout life. There are no data from randomized controlled trials of the clinical efficacy of diphtheria toxoid,

TABLE 1: EPIDEMIOLOGY OF THE 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 persons	As long as sputum has 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 Alcholism Diabetes
Diphtheria	Toxin producing bacterium (*C.diphtheriae*)	Humans	Close contact-respiratory or cutaneous	Usually <2 w Some chronic carriers	Common	Usually lifelong	Crowding, Low socio-economic status
Tetanus	Toxin producing bacterium (*Cl. tetani*)	Animal intestines, soil	Spores enter body through wounds / umbilical cord	No person-person transmission	No	No immunity induced by infection	Contamination of umbilical cord, Agriculture work
Pertussis	Bacterium (*B.pertussis*)	Humans	Close respiratory contact	Usually <3 w (starts before whoop is apparent)	Mild illness common, may not be diagnosed	Usually lifelong	Young age Crowding
Poliomyelitis	Virus (Serotypes 1, 2, 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 d before until 2 d after rash	May occur, but relative importance unknown	Lifelong	Crowding, Low socio-economic status
Yellow fever	Virus	Humans Monkeys	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 y	Common, especially in infants	If develops, lifelong	HBeAg+ mother, Multiple sexual partners; IVDU

but outbreak investigations have shown efficacies of over 87%[14].

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 (Lines flocculationis) 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 y 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 hyperactivity 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.

Tetanus toxoid:

Tetanus toxoid (TT) is a formaldehyde-inactivated preparation of tetanus toxin, adsorbed onto aluminium salts to increase the antigenicity. TT is stable and can withstand exposure to room temperature for months and 37° 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. 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%[15].

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[16]. 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[17]. Whole cell vaccine causes frequent local reactions and fever. Rarely, it may cause neurological reactions.

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 2 y of age and in December 1991 were licensed in the USA for booster dose of DPT in children aged 15 mo through 6 y[18]. Several clinical trials are now in progress to compare the efficacy of primary immunization of infants with DPT acellular and whole cell pertussis vaccines[3]. Meanwhile, the wide spread use of DPT vaccine containing the whole cell pertussis component remains the cornerstone of pertussis control.

Poliomyelitis vaccine:

There are two types of vaccine against poliomyelitis: oral and injectable. Oral poliomyelitis vaccine (OPV) is composed of three types of attenuated polio viruses (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, trivalent OPV is the vaccine of choice for eradication of poliomyelitis is recommended.

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 type1, 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[19]. 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.

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[20-22]. 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 fecal-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 mo and above. In developing countries, seroresponse rates and clinical efficacy have usually exceeded 85%[23].

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 y and often 30 y or more[24]. 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[25]. The vaccine is recommended for use from 6 mo of age and is most easily integrated into the EPI by administering it at the same time as measles vaccine (usually 9 mo). 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 y 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 (HBIG) at birth to the vaccine schedule may improve efficacy somewhat, but use of HBIG is not feasible in most developing countries. Table 2 presents general information on the nature of vaccines, their potency, form and route of administration, and Table 3 summarizes information on their immunogenicity and efficacy.

ADMINISTRATION OF VACCINES

Vaccines containing aluminium adjuvants (DPT, DT, TT, Td and hepatitis B vaccine) should be injected intramuscularly. Some Scandinavian and Eastern Europe countries practice 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

TABLE 2: CHARACTERISTICS OF 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 id	Medium in dried form, low in reconstituted form
Diphtheria	Toxoid	At least 30 IU	Fluid	$Al(OH)_3$/ $AlPO_4$	Usually merthiolate	3 im	High
Tetanus	Toxoid	At least 40 IU in TT and 60 IU for T component in DPT when tested in mice	Fluid	$Al(OH)_3$/ $AlPO_4$	Usually merthiolate	3 im	High
Pertussis	Killed whole cell pertussis bacterium	Atleast 4 IU	Fluid	$Al(OH)_3$/ $AlPO_4$	Usually merthiolate	3 im	Medium
Poliomyelitis	Attenuated live viruses of 3 types	Type 1: ≥ 1million Type 2: ≥ 100 000 Type3: ≥ 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 sc	Medium in dried form, low in reconstituted form
Yellow fever	Attenuated live virus	Atleast 1000 mouse LD_{50} or the equivalent in PFU	Freeze-dried	None	Stabilizing substances	1 sc	Medium in dried form, low in reconstituted form
Hepatitis B	HBsAg	2.5 to 20 mcg of HBsAg	Fluid	$Al(OH)_3$/ $AlPO_4$	Usually merthiolate	3 sc	High

IU: international units of potency as determined in animal tests; Infectious units: $CCID_{50}$ – cell culture infective dose 50%: the quantity of a virus suspension that will infect 50% of cell cultures; PFC – plaque forming units: the smallest quantity of a virus suspension that will produce a plaque in monolayer cell cultures; id: intradermal; im: intramuscular (some countries use deep subcutaneous injections); sc: subcutaneous

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. The immune response following a lower dose, especially of recombinant hepatitis B vaccine, may be reduced.

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[26] and has a high mortality rate in HIV-

TABLE 3: VACCINE EFFICACY AND VACCINE-INDUCED IMMUNITY

Vaccine	Vaccine efficacy	Nature of protective antibodies and protective and protective level of antibodies*	Duration of immunity after primary after primary series	Comments
BCG	0-80% vs lung TB 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 y; longer in presence of natural boosting	Recent trends to lower antibody levels in adults because of less natural boosting
Tetanus toxoid	>95% (>80% after two doses)	Antitoxin; 0.01 IU/ml by neutralization test	5 y	5 doses in adults provide over 20 y 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 immunity wanes with time	Lack immunological correlates of protection
Poliomyelitis	>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 mo of age; >85% at 9 mo of age	Neutralizing antibody; 200 m IU/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 y	Boosters required every 10 y for international travel
Hepatitis B	75-95%;efficacy higher against chronic carriage than against infection with the virus	Antibody to surface antigen 10 m IU/ml	>10 y;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.

positive children[27,28]. 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[29]. The HIV epidemic is leading to a dramatic increase in the global number of tuberculosis cases[30,31]. Information on the incidence and severity of the other target diseases in HIV-infected individuals is limited.

The safety of 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[32-36]. 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[37].

Isolated cases of disseminated BCG disease (generalized infection due to BCG) have been reported among infants with asymptomatic HIV infection[38-43]. 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[36,44]. There have, however, been reports of severe reactions in adults with symptomatic AIDS who received BCG vaccine[39,45]. 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 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[46]. However, in developing countries, adults have naturally-acquired immunity and the risk of paralysis in contacts is likely to be very low.

The immunogenicity of vaccines in HIV-infected individuals:

Most HIV-infected children have the capacity to mount both cellular and humoral immune responses during the first 2 y of life; decline in these responses occurs during the next 2 y[47]. Studies of the immunogenicity of vaccine have shown satisfactory seroconversion rates in the early stages of infection. However the proportion of responders decrease 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%)[36]. The response to measles vaccine is also lower in HIV-infected than non-infected infants[48,49], and is related to severity of infection. In a study in Zaire, among HIV-infected, asymptomatic HIV-infected and symptomatic HIV-infected children, 89%, 77% and 36%, respectively seroconverted after Schwarz vaccine at age 9 mo[49]. Antibody levels induced by the vaccines tend to be lower in HIV-infected individuals and to fall more rapidly over time than in non-infected persons[35,36]. 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[37].

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. 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.

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[50-54] (Table 4). It is recommended that individuals with known or suspected asymptomatic HIV infection receive all 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 mo of age with a second dose as soon after age 9 mo as possible[54]. Individuals with symptomatic HIV infection can receive all vaccines except BCG and yellow fever vaccines. 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 mo of age with a second dose at 9 mo. Children with known or suspected HIV infection should be considered to be in this high-risk category and receive measles vaccine at 6 mo of age, followed by a second dose at 9 mo[54].

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 vaccines in a limited interval after immunization, or
- If vaccines 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. It is recommended that all immunization programmes should monitor adverse events following immunization. A field guide for surveillance of adverse effects has been produced[55]. 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.

CONCLUSIONS

There is an urgent need for development of new vaccines. No successful vaccine against any human parasite has yet been developed. In developing countries, those most at risk of enteric infections and diarrheal diseases are infants and young children. The pace of vaccine research and development has quickened with better understanding of the antigens responsible for disease and protection, and with the advent of powerful molecular and cell biological techniques. We are now 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[56].

TABLE 4: 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 w
OPV*	Yes	Yes	0, 6, 10, 14 w
Measles	Yes	Yes	6 and 9 mo
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.

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