# Immunization of children at risk of infection with human immunodeficiency virus

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**Abstract** This paper reviews the English language literature on the safety, immunogenicity and effectiveness in children infected with the human immunodeficiency virus (HIV) of vaccines currently recommended by WHO for use in national immunization programmes. Immunization is generally safe and beneficial for children infected with HIV, although HIV-induced immune suppression reduces the benefit compared with that obtained in HIV-uninfected children. However, serious complications can occur following immunization of severely immunocompromised children with bacillus Calmette–Guérin (BCG) vaccine. The risk of serious complications attributable to yellow fever vaccine in HIV-infected persons has not been determined.

WHO guidelines for immunizing children with HIV infection and infants born to HIV-infected women differ only slightly from the general guidelines. BCG and yellow fever vaccines should be withheld from symptomatic HIV-infected children. Only one serious complication (fatal pneumonia) has been attributed to measles vaccine administered to a severely immunocompromised adult. Although two HIV-infected infants have developed vaccine-associated paralytic poliomyelitis, several million infected children have been vaccinated and the evidence does not suggest that there is an increased risk. The benefits of measles and poliovirus vaccines far outweigh the potential risks in HIV-infected children. The policy of administering routine vaccines to all children, regardless of possible HIV exposure, has been very effective in obtaining high immunization coverage and control of preventable diseases. Any changes in this policy would have to be carefully examined for a potential negative impact on disease control programmes in many countries.

**Keywords** HIV infections/immunology; BCG vaccine/immunology/adverse effects; Measles vaccine/immunology; Poliovirus vaccine, Oral/immunology; Yellow fever vaccine/immunology/adverse effects; Diphtheria-tetanus-pertussis vaccine/immunology; Hepatitis B vaccines/immunology; Haemophilus vaccines/immunology; Infant; Immunization programs; Guidelines; World Health Organization; Review literature (*source: MeSH, NLM*).

**Mots clés** HIV, Infection/immunologie; Vaccin BCG/immunologie/effets indésirables; Vaccin antimorbilleux/immunologie; Vaccin antipoliomyélitique Sabin/immunologie; Vaccin anti-fièvre jaune/immunologie/effets indésirables; Vaccin diphtérie-tétanos-coqueluche/immunologie; Vaccin antihépatite B/immunologie; Vaccin antihémophilus/immunologie; Enfant; Nourrisson; Programmes de vaccination; Lignes directrices; Organisation mondiale de la Santé; Revue de la littérature (*source: MeSH, INSERM*).

**Palabras clave** Infecciones por VIH/inmunología; Vacuna BCG/inmunología/efectos adversos; Vacuna antisarampión/inmunología; Vacuna antipolio oral/inmunología; Vacuna contra la fiebre amarilla/inmunología/efectos adversos; Vacuna difteria-tétano-pertussis/inmunología; Vacunas contra hepatitis B//inmunología; Vacunas contra haemophilus/inmunología; Vacunas bacterianas/inmunología; Vacunas virales/inmunología; Vacunas atenuadas/inmunología; Niño; Lactante; Programas de inmunización; Pautas; Organización Mundial de la Salud; Literatura de revisión (*fuente: DeCS, BIREME*).

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*Voir page 68 le résumé en français. En la página 68 figura un resumen en español.*

## Introduction

The majority of children born to women who are infected with human immunodeficiency virus (HIV) do not acquire HIV infection. Of those children who do become infected, most acquire the virus from their mothers at the time of delivery or shortly thereafter. Early in life they are immunologically normal but, in the absence of specific therapy for HIV infection, develop progressive immunodeficiency that affects all aspects of the immune system. The rate of progression to clinically apparent immunosuppression depends on maternal, infant, and viral factors. Accordingly, the safety and effectiveness of vaccines in HIV-infected children varies with age at vaccination and their immune status.

Guidelines for administering immunizations usually make special provisions for children known to have underlying immunodeficiency disorders. The following areas of concern are critical to the development of such guidelines.

- Will the effectiveness of a vaccine be impaired because of underlying immune deficiency?
- Are persons receiving a live viral vaccine or a bacterial vaccine subject to a significantly increased risk compared with non-infected persons?
- Does administering a vaccine significantly affect the rate of HIV-associated disease?

In this paper we review the literature published in English on the safety, immunogenicity and effectiveness of vaccines, including new vaccines that are being introduced in some areas, and critically evaluate WHO's recommendations on the vaccination of HIV-infected persons.

# Current WHO recommendations for immunization of children with known or suspected HIV infection

Few adverse events have been observed following the immunization of HIV-infected infants. Consequently, the current WHO guidelines for immunizing children known to have HIV infection and infants born to HIV-infected women differ only slightly from the general guidelines for other infants (1). WHO's policy is based on the potential severity of vaccine-preventable diseases in HIV-infected children, on vaccine safety and immunogenicity, and on the degree of HIV-induced immunosuppression. Children with known or suspected asymptomatic HIV infection should receive all recommended vaccines in accordance with nationally recommended schedules subject to the modifications listed below.

- An extra dose of measles vaccine is recommended at 6 months of age in order to provide protection at a younger age than for non-HIV-infected infants and to improve protection against measles.
- Individuals with symptomatic HIV infection should not receive live attenuated BCG vaccine. Administration of BCG vaccine to HIV-exposed infants should be based on the risk of tuberculosis. If this risk is high, BCG vaccine should be administered at birth to children with possible HIV infection according to the standard schedule of the Expanded Programme on Immunization. If BCG vaccine remains on the schedule of a national immunization programme and the risk of tuberculosis is low, this vaccine should not be administered to children with suspected HIV infection.

- Individuals with symptomatic HIV infection should not receive live attenuated yellow fever vaccine.

# Immunogenicity and effectiveness
## Non-replicating vaccines
### Diphtheria–tetanus–pertussis vaccine
Following primary immunization in infancy, 40–100% of symptomatic and asymptomatic HIV-infected children respond to diphtheria and tetanus toxoids by developing protective levels of diphtheria and tetanus antitoxins (Table 1). However, HIV-infected children and adults develop lower geometric mean antitoxin titres and are more likely than uninfected persons to lose antibody within a few years after vaccination. Some studies have correlated antibody titres with CD4+ T-lymphocyte counts (Table 1). Comparable data for pertussis vaccines are more limited and their interpretation is more difficult since serological correlates of protection have not been identified. The available data suggest that the proportion of children who seroconvert and the geometric mean antibody titres to pertussis toxin are lower for HIV-infected children than for healthy controls (2). There is no evidence that HIV-infected children have higher vaccine failure rates than HIV-uninfected children following diphtheria, tetanus or pertussis immunization, but there have been no rigorous studies of the effectiveness of diphtheria–tetanus–pertussis vaccine in HIV-infected children.

### Hepatitis B vaccines
The serological response to hepatitis B vaccines is lower for HIV-infected children and adults than for uninfected persons of similar age (Table 2). Serological response rates have varied, but most studies have reported that only 25–50% of HIV-infected children have developed protective antibodies. As with tetanus and diphtheria toxoids, response rates appear to be higher for younger children and in some studies correlate

Table 1. **Immunogenicity of diphtheria and tetanus toxoids and pertussis vaccines in children and adults infected with human immunodeficiency virus (HIV)**

| Vaccine | Author (year of publication)[a] | Country | No. of subjects | Age | % of HIV-infected persons developing protective antibody titres |
|---|---|---|---|---|---|
| **Tetanus toxoid** | Bernstein (1986) | USA | 5 | 2–6 years | 40%; titres lower than in controls |
| | Blanche (1986) | France | 13 | 1–24 months | 62%; lower titres in children with opportunistic infections |
| | Ballet (1987) | France | 25 | Adults | 77%; no difference in geometric mean titre from controls |
| | Opravil (1991) | Switzerland | 10 | Adults | Increase in geometric mean titre; correlated with CD4 cell counts |
| | Barbi (1992) | Italy | 17 | 18–84 months | 77%; titres lower than in controls |
| | Kroon (1994) | Netherlands | 47 | Adults | 84%; correlated with CD4 cell counts |
| | Talesnik (1998) | Chile | 26 | Adults | 23%; decline in antibody titres at 1 year |
| **DTP[b]** | Borkowsky (1987) | USA | 17 | 11–90 months | 60% to tetanus; 18% to diphtheria; cell-mediated immunity in some children without protective antibody titres |
| | Borkowsky (1992) | USA | 37 | < 4 years | 91% to tetanus; 76% to diphtheria; better responses early in life |
| | Ryder (1993) | Zaire | 48 | < 4 months | 96% to tetanus; 71% to diphtheria; titres lower than in controls |
| **Acellular pertussis** | DeMartino (1997) | Italy | 12 | 6–107 months | 75%; titres lower than in controls; correlated with CD4 cell counts |

[a] Full references available on request.
[b] DTP = diphtheria– tetanus–pertussis vaccine.

Table 2. **Immunogenicity of hepatitis B vaccines in children and adults infected with human immunodeficiency virus (HIV)**

| Author (year of publication)[a] | Country | Vaccine and dose | No. of subjects | Age | % of HIV-infected persons developing protective antibody titres |
|---|---|---|---|---|---|
| Zuin (1993) | Italy | Engerix-B[b] (20 μg) | 18 | 2 neonates 16 children | 78%; titres lower than in controls; no correlation with CD4 cell count; poor response to booster dose |
| Diamant (1993) | USA | <11 years: Engerix-B (10 μg) or Recombivax HB[c] (2.5 μg) >11 years: Engerix-B (20 μg) or Recombivax HB (5 μg) | 24 | 5–115 months | 25%; correlated with CD4 cell count |
| Rutstein (1994) | USA | Recombivax HB (2.5 μg) | 17 | 1 day to 4 months | 35%; no correlation with CD4 cell count |
| Zuccotti (1994) | Italy | Engerix-B (20 μg) | 5 | 2–6 months | 20% |
| Arrazola (1995) | Spain | Engerix-B (10 μg) | 17 | 10 neonates 7 children: 1–63 months | 41%; no correlation with CD4 cell count |
| Choudhury (1995) | USA | Booster doses <11years: Engerix-B (20 μg) >11years: Engerix-B (40 μg) | 14[d] | 21–30 months | 14%; 0 of 7 developed antibody response after second booster dose |
| Scolfaro (1996) | Italy | Engerix-B (10 μg) | 20 | 1–102 months | 45%; not correlated with CD4 cell count; 73% of 11 responded to booster (20 μg) |
| Collier (1988) | USA | Plasma-derived | 16 | Adults | 56%; titres lower than in controls |
| Keet (1992) | Belgium | Recombinant | 32 | Adults | 28%; titres lower than in controls |
| Bruguera (1992) | Spain | Recombinant | 21 | Adults | 24%; titres lower than in controls |
| Tayal (1994) | United Kingdom | Engerix-B (20μg) | 12 | Adults | 17%; poor response to additional dose |
| Wong (1996) | Australia | Plasma-derived or recombinant | 14 | Adults | 43% |
| Rey (2000) | France | Genhevac B (20 μg)[e] | 20 | Adults | 55% after 3 injections; 78% of 9 non-responders after 3 additional doses |

[a] Full references available on request.
[b] GlaxoSmithKline, Research Triangle Park, NC 27709, USA.
[c] Merck, West Point, PA , USA.
[d] Follow-up study of children previously reported in Diamant (1993).
[e] Pasteur–Mérieux Serums & Vaccins, 92430 Marnes La Coquette, France.

with CD4+ T-lymphocyte counts. Attempts to overcome the decreased response by administering higher doses or extra doses of hepatitis B vaccine have not been promising in children (*3*, *4*). However, one study of 20 HIV-infected adults reported that seven of the nine individuals who failed to respond to the initial three-dose series developed a protective antibody response after three additional doses of hepatitis B vaccine (*5*). HIV-infected children and adults who respond to hepatitis B vaccine have a more rapid decline in antibody titre than uninfected persons. For example, only 42% of HIV-infected children who seroconverted after the primary three-dose series or after receipt of the adult dose of hepatitis B vaccine had protective antibody titres 13–18 months after immunization (*6*). Long-term follow-up studies suggest that most HIV-uninfected children and adults have continued protection against becoming clinically ill and chronic HBsAg carriers after exposure, despite loss of detectable antibody (*7*). It is not known whether such protection occurs in HIV-infected persons with undetectable antibody levels. In immunologically normal persons, however, loss of detectable antibody after developing a protective antibody response ($\geqslant$ 10 mIU) does not mean that protection against hepatitis B has been lost.

## Polysaccharide and polysaccharide–protein conjugate vaccines

In the absence of acquired immunodeficiency syndrome (AIDS) or profoundly diminished CD4+ T-lymphocyte counts, 37–86% of HIV-infected children developed protective antibody responses to *Haemophilus influenzae* type b conjugate vaccine, but the geometric mean titres were lower than those reported for HIV-uninfected persons of similar ages (*8–12*). Antibody levels decline more rapidly in HIV-infected children but booster doses of vaccine induce rapid increases in the levels, suggesting the retention of immunological memory in many HIV-infected children (*11*). One study reported that antibody titres decreased to below 1 μg/ml in 43% of 48 HIV-infected children one year after vaccination, whereas the corresponding proportion was only 11% for HIV-uninfected children (*10*). The absence of high rates of vaccine failure among HIV-infected children in settings where routine immunization has been introduced suggests that many such children are protected against invasive disease following immunization with conjugate *H. influenzae* type b vaccines.

No data are available on the response of HIV-infected children or adults to meningococcal polysaccharide or

conjugate vaccines, but the response to 23-valent pneumococcal polysaccharide vaccine is poorer than that of HIV-uninfected persons. The antibody response to a glycoprotein conjugate pneumococcal vaccine was better than that of the polysaccharide vaccine in HIV-infected persons, except for those with very low CD4+ T-lymphocyte counts (13, 14). Since polysaccharides are processed as T-independent antigens, the immune response is not affected by HIV-induced impairment of the immune response to the same extent as with T-dependent antigens. However, the antibody response to specific pneumococcal polysaccharide serotypes varies, some serotypes eliciting poor antibody responses in HIV-infected persons with CD4+ T-lymphocyte counts below 200 cells/mm$^3$ (15). In HIV-infected Ugandan, adults the 23-valent pneumococcal polysaccharide vaccine did not prevent first episodes of invasive pneumococcal disease (16).

## Live bacterial vaccines

### Bacillus Calmette–Guérin (BCG) vaccine
The tuberculin skin test is the only practical tool for determining the response to BCG vaccination, but the diameter of the skin test following immunization is not a good predictor of protection against *Mycobacterium tuberculosis* disease. In Rwanda, only 37% of HIV-infected infants developed a skin test response exceeding 6 mm in diameter after BCG vaccination, whereas the corresponding proportions for HIV-uninfected infants born to HIV-infected women and for infants born to HIV-uninfected women were 57% and 70%, respectively (17).

The protection conferred by BCG vaccination against tuberculous meningitis and miliary tuberculosis in HIV-uninfected populations varies widely, most probably because of differences in BCG strains and in study methodologies, but a recent meta-analysis indicated that the overall protection was approximately 80% (18). In Zambia the proportion of children

with BCG scars (83%) was the same for 30 HIV-infected children with tuberculosis and for 18 such children who did not have tuberculosis, i.e. there was no evidence of protection from BCG vaccination (19). This study did not have sufficient power to evaluate protection against tuberculous meningitis or miliary disease. Studies of tuberculosis in adults who had received BCG vaccine in infancy have not shown a clear protective benefit (20, 21). These data are not adequate to permit definitive conclusions about the effectiveness of BCG vaccine to protect HIV-infected children or adults against tuberculosis.

## Live viral vaccines

### Oral poliovirus vaccine (OPV)
The proportion of HIV-infected children who responded to three doses of OPV exceeded 90% in most studies (Table 3). In the Democratic Republic of Congo (formerly Zaire), 97% of HIV-infected children developed protective antibody titres to poliovirus types 1, 2, and 3 after three doses of OPV (22). However, this study was conducted when there was widespread circulation of wild-type polioviruses, which could have contributed to the high proportion of children with antibody. Although no direct estimates of the efficacy of poliovirus vaccine have been conducted in HIV-infected children, wild-type polioviruses have been eliminated from several countries with high prevalence rates of HIV infection.

### Measles virus vaccine
Antibody response to measles vaccine is impaired in HIV-infected persons (Table 4). Approximately one-fourth to one-third of HIV-infected children have responded to a single dose of standard-titre measles vaccine in most prospective studies (23–26). In a study of HIV-seropositive children in Zaire, 65% had protective titres of measles antibody three months after measles vaccination at 9 months of age; only 36% of

Table 3. **Immunogenicity and safety of poliovirus vaccines in children infected with human immunodeficiency virus (HIV)**

| Author (year of publication)[a] | Country | Vaccine[b] | No. of subjects | Age | Safety | % of HIV-infected persons developing protective antibody titres |
|---|---|---|---|---|---|---|
| Blanche (1986) | France | OPV | 15 | 1–24 months | No adverse events | 40% to type 2; 33% to types 1 and 3 |
| Krasinski (1987) | USA | OPV | 23 | 1–180 months | No adverse events | 91%; lower titres with advanced disease |
| McLaughlin (1988) | USA | OPV | 180 | 1–132 months | No adverse events | Immunogenicity not studied |
| Barbi (1992) | Italy | IPV | 9 | 4–42 months | No adverse events | 100% to types 1 and 2; 88% to type 3 |
| Barbi (1992) | Italy | OPV/IPV | 12 | 18–84 months | No adverse events | 100% to type 2; 92% to types 1 and 3; decrease in titres over 2 years in 4 children studied |
| Ryder (1993) | Zaire | OPV | 48 | < 4 months | No adverse events | 97%; titres lower than controls |
| Ion-Nedelcu (1994) | Romania | OPV | 1 | 26 month | Flaccid paralysis with vaccine poliovirus type 2 | Lacked protective antibody titres to all three types despite receipt of four doses of OPV |
| Chitsike (1999) | Zimbabwe | OPV | 1 | 4 years | Paralysis of right leg two weeks after second dose of OPV | Lacked antibodies to polioviruses types 1 and 3 despite having received OPV during first year of life |

[a] Full references available on request.
[b] OPV = oral poliovirus vaccine; IPV = inactivated poliovirus vaccine.

Table 4. **Prospective studies on the immunogenicity of measles vaccine in children infected with human immunodeficiency virus (HIV)**

| Author (year of publication)[a] | Country | No. of children | Age | Response to primary immunization | Response to repeat immunization |
|---|---|---|---|---|---|
| Oxtoby (1989) | Zaire | 37 | 9 months | 36% of 11 symptomatic 77% of 26 asymptomatic | NA[b] |
| Krasinski (1989) | USA | 8 | 11–41 months | 25% | NA |
| Palumbo (1992) | USA | 35 | 12–194 months | 37% | 0% |
| Brena (1993) | USA | 2 | NA | NA | 50% |
| Frenkel (1994) | USA | 4 | 22–121 months | NA | 0% |
| Brunell (1995) | USA | 11 | 72–120 months | NA | 36% |
| Arpadi (1996) | USA | 7 | 31–120 months | NA | 14% |
| Thaithumyanon (2000) | Thailand | 16 | 9 months | 57% | NA |

[a] Full references available on request.
[b] NA = information not available.

11 symptomatic children seroconverted, whereas 77% of 26 asymptomatic children did so (*23*). The response to a second dose of vaccine varied but was generally poor (*25, 27–30*). In cross-sectional studies there were wide variations in the age at immunization, the number of vaccine doses received, the interval between immunization and assay, the type of measles antibody assay, and the degree of immunosuppression at the time of assessment. In children, the prevalence of measles antibody varied from 17% to 100%, with a median value of 60% (*24, 25, 27, 29–33*). Most HIV-infected adults, however, were seropositive for measles antibodies (*34, 35*). An association between lack of measles-specific antibodies after vaccination and low CD4+ T-lymphocyte counts (< 600 cells/mm$^3$) was documented in one prospective study (*25*) and two cross-sectional studies (*30, 33*). In a study of Ugandan children, a poor antibody response to measles vaccine was associated with stunting but not with HIV infection (*36*). HIV-infected children appear to experience a more rapid decline in measles antibodies than HIV-uninfected children (*30*), the median time to loss of antibody detectable by enzyme immunosorbent assay was 30 months in a study of 17 HIV-infected children (*33*).

Placental transfer of maternal antibodies, including antibodies to measles, may be impaired in HIV-infected women (*32, 37, 38*). The lower amounts of maternal antibody correlated with an improved response to standard-titre measles vaccine administered at 6 months of age. Less immunosuppression at 6–9 months of age may contribute to higher response rates than at 12–15 months of age (*32*). Studies in progress are evaluating the immunogenicity of measles vaccination at 6 and 9 months of age in HIV-infected children.

Experience in southern Africa suggests that the number of measles cases can be reduced in regions of high HIV prevalence by maintaining high immunization rates coupled with periodic supplemental campaigns (*39*). However, primary and secondary vaccine failures in HIV-infected children and the potential for prolonged measles virus shedding (*40*) could hinder the long-term control or elimination of measles in regions of high HIV prevalence.

### Yellow fever virus vaccine
Limited data suggest that HIV-infected children respond poorly to yellow fever vaccine (*41*). However, seroconversion rates were high in HIV-infected adults who were not severely immunocompromised (*42*). Only 3 of 18 HIV-infected children (17%) developed an antibody response to yellow fever vaccine, whereas 74% of 57 HIV-uninfected children did so (*41*). No data are available on protection against disease following yellow fever vaccination of HIV-infected persons. Despite the possibility of reduced protection, it seems justifiable to encourage the use of the vaccine even in areas of high HIV prevalence.

## Safety of vaccines in HIV-infected persons
### Non-replicating vaccines
Non-replicating vaccines are not associated with increased risks of complications in immunocompromised persons. However, a study of HIV-infected Ugandan adults found a higher incidence of pneumonia among recipients of 23-valent pneumococcal polysaccharide vaccine than among unvaccinated HIV-infected adults (*16*). The authors hypothesized that immunization might result in the destruction of polysaccharide-responsive B-cell clones but presented no specific data to support this suggestion. Additional studies are needed on this issue.

### BCG vaccine
Complications arising from BCG vaccination include regional, extraregional localized, and disseminated disease. The rates of these complications in HIV-uninfected children vary. BCG causes local ulcers and regional lymphadenitis in normal hosts at rates varying from 4 to 30 per 1000 vaccinated infants, depending on the vaccine strain, the technique of administration, and the dose (*43*). There are several reports of regional lymphadenitis, poorly healing ulcers, and fistulae in HIV-infected infants (Table 5). Administration of BCG to HIV-infected children in the first month of life is associated with relatively low rates of complications because immune suppression takes several months to develop. In direct comparisons, the rates of these complications have been similar in HIV-infected and HIV-uninfected infants, but lymphadenitis has been more severe in HIV-infected children.

More than 28 cases of disseminated BCG infection have been reported in HIV-infected children and adults (Table 5) (*44, 45*). Because the diagnosis cannot be made on

Table 5. **Adverse events associated with BCG vaccination in children infected with human immunodeficiency virus (HIV)**

| Author (year of publication)[a] | Country | Study population | Adverse events[b] |
|---|---|---|---|
| Blanche (1986) | France | 18 HIV-infected | Disseminated BCG infection in 3 (17%) |
| Carswell (1987) | Uganda | 54 children born to HIV-infected women | No complications |
| Bregere (1988) | France | 67 HIV-infected | BCG lymphadenitis in 7 (10%) |
| Houde (1988) | Canada | 1 HIV-infected | Disseminated BCG infection in a 2-month-old girl |
| Ninane (1988) | Belgium | 1 HIV-infected | Disseminated BCG infection in a 4-month-old boy from Zaire |
| Hira (1989) | Zambia | 42 HIV-infected children | BCG lymphadenitis in 1 (3%) |
| ten Dam (1990) | Switzerland | 1 HIV-infected | Disseminated BCG infection in an 8-month-old girl from Argentina |
| Lallemant (1991) | Congo | 21 HIV-infected | BCG lymphadenitis in 5 (24%) |
| MMWR (1991) | Rwanda | 37 HIV-infected | BCG lymphadenitis in 2 (5%) |
| Green (1992) | Zaire | 21 HIV-infected | No complications |
| Ryder (1993) | Zaire | 48 HIV-infected 640 HIV-uninfected | Lymphadenitis in 5% HIV-infected and 3.5% HIV-uninfected Fistulae in 5% HIV-infected and 6 to 8% HIV-uninfected |
| Besnard (1993) | France | 68 HIV-infected | 4 with BCG lymphadenitis, 3 with fistula, 2 with disseminated BCG (13%) |
| O'Brien (1995) | Haiti | 13 HIV-infected | BCG lymphadenitis, ulceration or abscess in 4 (31%); double dose of BCG |
| Edwards (1996) | USA | 1 HIV-infected | BCG bacteraemia in a 3-year-old HIV-infected Brazilian girl |
| Sharp (1999) | Australia | 1 HIV-infected | BCG lymphadenitis |
| Thaithumyanon (2000) | Thailand | 26 HIV-infected | No complications |

[a] Full references available on request.
[b] BCG = bacillus Calmette–Guérin vaccine.

clinical criteria alone and requires laboratory facilities to culture the organism and differentiate it from other mycobacteria, this complication has undoubtedly occurred in more HIV-infected individuals than has been reported in the published literature. Although disseminated disease usually occurs between several months and a few years following vaccination, it was reported in one 30-year-old with HIV infection who received BCG vaccine at birth (46). Disseminated BCG infection is more likely to occur when the vaccine is administered to individuals with clinical AIDS or advanced immunosuppression. Progressive immune suppression can lead to the reactivation of latent BCG organisms, causing regional or disseminated disease (46, 47). In one study, however, no cases of disseminated BCG infection were found among 155 adult patients with AIDS who had received BCG vaccine in infancy and whose blood was cultured for mycobacteria (21).

## Live viral vaccines
### Oral poliovirus vaccine
The risk of vaccine-associated paralytic poliomyelitis is increased in persons with primary B cell immunodeficiency disorders. Nevertheless, in the USA more than 1000 HIV-infected children received at least one dose of OPV without complications before it was known that they or their mothers were HIV-infected, and several thousand HIV-infected children in other countries have been vaccinated. We estimate that, in the 20 years since the HIV epidemic has been

recognized, more than 500 000 HIV-infected children have received one or more doses of OPV. Only two HIV-infected children have been reported with vaccine-associated paralytic poliomyelitis following the receipt of OPV (Table 3): a 2-year-old Romanian girl (48) and a child in Zimbabwe (49). In Romania the rate of vaccine-associated paralytic poliomyelitis in all children was approximately ten times higher than the estimated 1 case per 2.5 million doses administered in the USA and Europe, most probably because of the use of multiple injections (50). The HIV infections in these two children with vaccine-associated paralytic poliomyelitis could be chance associations and not evidence of an increased risk associated with HIV infection. If the risk of vaccine-associated paralytic poliomyelitis is greater for HIV-infected persons, the attributable risk is very low. Studies in progress are evaluating the possibility of prolonged excretion of poliovirus vaccine strain by HIV-infected children.

### Measles virus vaccine
Prospective studies revealed that the risk of adverse events in the few weeks following immunization with standard-titre and high-titre measles vaccines was no different for HIV-infected and HIV-uninfected children (51), although one HIV-infected adult developed fever, rash, coryza and conjunctivitis 12 days after measles immunization (52). A retrospective survey conducted by the New York City Department of Health found no complications following measles immunization of

HIV-infected children (*53*). Measles vaccine virus was detected by means of the polymerase chain reaction in a 14-month-old HIV-infected boy who developed diarrhoea and a febrile illness associated with a 4-day generalized rash after receiving measles–mumps–rubella vaccine (*54*). No evidence of persistent excretion of measles vaccine virus was found in 10 HIV-infected children immunized with this vaccine (*28*).

Only one serious adverse event has been reported following the administration of measles vaccine to an HIV-infected person (*55*). A 20-year-old HIV-infected man, who had a very low CD4+ T-lymphocyte count at the time he received a second dose of measles–mumps–rubella vaccine, developed cough and progressive pulmonary infiltrates 10 months after immunization. An open lung biopsy showed giant cell pneumonitis, and measles vaccine virus was identified in the lung tissue. The patient died several months later from the progressive pneumonitis

### Yellow fever vaccine
WHO became concerned about the theoretical risk of yellow fever vaccine causing illness in immunocompromised individuals and about early unconfirmed reports of serious adverse events in HIV-infected persons and issued guidelines on avoiding the use of yellow fever vaccine in symptomatic HIV-infected individuals (*1*). Few severe complications attributable to the inadvertent immunization of immunocompromised individuals with yellow fever vaccine have been reported, but experience is limited. Fatal myeloencephalitis caused by yellow fever vaccine was reported in a 53-year-old HIV-infected man in Thailand (*56*), although no adverse events were observed following yellow fever vaccination of two HIV-infected adults (*57*). Seven cases of severe illness resembling yellow fever, six of them fatal, were reported with evidence of vaccine virus in affected tissues, but there was no evidence of HIV infection (*58*). These findings are encouraging but more studies are needed in order to confirm the safety of yellow fever vaccine in HIV-infected persons. On the basis of the available information, the authors consider that, in the event of an outbreak, yellow fever vaccine should be administered to the whole population at risk, irrespective of their HIV infection status. Travel clinics for healthy adults are generally more conservative, and administer yellow fever vaccine only to those with adequate CD4+ T-lymphocyte counts.

## Effect of vaccination on HIV disease progression
The activation of CD4+ T-lymphocytes following immunization could potentially augment HIV replication and result in accelerated progression to disease. Several, but not all investigators (*59*) have described increased HIV RNA plasma levels lasting several days following immunization with tetanus toxoid (*60*) and with influenza (*61–64*), pneumococcal (*65, 66*) and hepatitis B vaccines (*5, 67*). Importantly, no investigators have observed prolonged elevation of HIV RNA viral load, decreased CD4+ lymphocyte counts or accelerated HIV disease progression following immunization (*68*). Although the transient rise in HIV viral load following the administration of tetanus toxoid to pregnant women could theoretically affect the risk of maternal–infant HIV transmission, an increased risk of transmission is unlikely if vaccination occurs at least four weeks before delivery.

## Conclusions
The current WHO recommendations for the vaccination of HIV-infected children and adults are appropriate. However, the factors discussed below should be taken into consideration.

### Timing of immunizations
Because of the decreased immune response to vaccines with increasing age in HIV-infected children, immunization should take place as early in life as possible in children born to HIV-infected women. For hepatitis B vaccine, early immunization is especially important because the risk of becoming a chronic carrier is higher for HIV-infected children and adults than for uninfected persons (*69*). A preference for immunization at birth should be indicated in countries with a high maternal HIV infection rate as well as in those where there are high rates of perinatal hepatitis B transmission. The limited available data do not suggest that there is a need for administering extra doses of hepatitis B vaccine to HIV-infected children.

### BCG vaccine
Most infants born to HIV-infected women do not acquire HIV infection. BCG vaccine provides some protection against severe disease for children in areas of high risk for tuberculosis. If it were possible to administer BCG vaccine only to HIV-uninfected children in the first month of life, the incidence of severe complications from this vaccine could be reduced. However, in most areas it is not practical at this time to identify HIV-infected children early in their lives. The current policy of administering BCG vaccine to all asymptomatic infants at risk of acquiring tuberculosis is appropriate. In regions where the risk of contracting tuberculosis is low, BCG vaccine should not be administered to children with known or suspected HIV infection.

### Poliovirus vaccine
It is not necessary or practical to consider the use of inactivated poliovirus vaccine for children born to HIV-infected women in most countries. Some countries that have been free of wild-type polioviruses for many years routinely use inactivated poliovirus vaccine to vaccinate HIV-infected children. In order to avoid the possible increased risk of vaccine-associated

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Box 1. **Research needs**
*Studies are needed on:*
- Whether the rate of perinatal HIV transmission is increased by the administration of tetanus toxoid to HIV-infected women late in the third trimester.
- The safety and effectiveness of polysaccharide and protein-conjugate pneumococcal and *Haemophilus influenzae* type b vaccines in HIV-infected persons.
- The duration of excretion of polioviruses by HIV-infected children.
- The risk of flaccid paralysis from poliovirus vaccine in children with advanced HIV disease.
- The immunogenicity of measles vaccine in HIV-infected children, administered as early as 6 months of age, and whether measles vaccine failures in HIV-infected children contribute to continued transmission of measles in highly immunized communities.
- The risk of disease caused by measles vaccine virus in children with advanced HIV disease, especially during mass measles immunization campaigns.
- The safety and immunogenicity of yellow fever vaccine in HIV-infected children.

paralytic poliomyelitis, countries where wild-type polioviruses have been eliminated may consider the use of inactivated poliovirus vaccine for immunocompromised HIV-infected children if the necessary resources are available.

## Measles vaccine
Immunocompromised HIV-infected children are at risk of death or severe complications following wild-type measles virus infection. The balance of risk clearly favours measles immunization in regions where there is transmission of wild-type measles virus. If measles virus is circulating in a community, all children, regardless of HIV infection status, should receive measles vaccine. Current WHO policy adequately addresses the need for early measles immunization of children born to HIV-infected women. Although definitive evidence is lacking, an extra dose of standard-titre measles vaccine administered to HIV-infected infants at 6 months of age is likely to result in protective antibody titres because inhibitory maternal antibody titres are low and the immune system is still unimpaired.

Where the chance of contracting wild-type measles virus infection is almost non-existent, countries with the capacity to monitor an individual's immune status may consider withholding measles vaccine from severely immunocompromised HIV-infected children. Children with moderate levels of immune suppression should continue to receive measles vaccine.

## Yellow fever vaccine
Yellow fever vaccine should be withheld from HIV-symptomatic individuals until more information is available on the vaccine's safety for HIV-infected individuals.

## Research
Research in several areas (see Box 1) is needed in order to further evaluate and consider future modifications of WHO policies for the vaccination of HIV-infected persons. ■

## Résumé

### Vaccination de l'enfant à risque d'infection par le virus de l'immunodéficience humaine

L'article passe en revue la littérature de langue anglaise concernant l'innocuité, l'immunogénicité et l'efficacité des vaccins actuellement recommandés par l'OMS dans le cadre des programmes nationaux de vaccination. La vaccination est en général sans danger et bénéfique chez l'enfant infecté par le virus de l'immunodéficience humaine (VIH) ; l'immunodépression induite par le VIH diminue cependant le bénéfice, comparé à celui obtenu chez des enfants indemnes d'infection. Le risque de complications graves est toutefois possible après vaccination par le bacille de Calmette et Guérin (BCG) quand l'enfant est gravement immunodéprimé. Le risque de complication post-vaccinale grave après vaccination antiamarile de personnes infectées par le VIH n'a pas été déterminé.

Les recommandations de l'OMS pour la vaccination de l'enfant atteint d'infection à VIH et du nourrisson né de mère infectée par le virus diffèrent très peu des recommandations générales. Le vaccin antiamaril et le BCG ne seront pas administrés à l'enfant symptomatique. Un seul cas de complication grave (pneumonie fatale) a été attribué au vaccin antirougeoleux administré à un adulte massivement immunodéprimé. Si deux nourrissons infectés par le VIH ont fait une poliomyélite paralytique post-vaccinale, plusieurs millions d'enfants infectés par le VIH ont été vaccinés et les données n'indiquent pas qu'il y ait augmentation du risque. Les avantages des vaccins antirougeoleux et antipoliomyélitique dépassent largement les risques potentiels chez ces enfants. La politique consistant à administrer les vaccins classiques à tous les enfants, quelle que soit leur exposition au VIH, a permis d'obtenir une bonne couverture vaccinale et la maîtrise de maladies évitables. Toute modification de cette politique devra être soigneusement pesée en raison de l'impact négatif qu'elle pourrait avoir dans de nombreux pays sur les programmes de lutte contre les maladies.

## Resumen

### Inmunización de los niños en riesgo de infección por el virus de la inmunodeficiencia humana

En este artículo se examina la literatura en inglés sobre la seguridad, inmunogenicidad y eficacia de las vacunas actualmente recomendadas por la OMS para los programas nacionales de vacunación. La inmunización es por lo general segura y beneficiosa para los niños infectados por el virus de la inmunodeficiencia humana (VIH), si bien la inmunodepresión causada por dicho virus atenúa los efectos beneficiosos en comparación con los conseguidos en los niños no infectados por el VIH. Sin embargo, los niños gravemente inmunodeprimidos pueden sufrir graves complicaciones tras la inmunización con la vacuna basada en el bacilo de Calmette-Guérin (BCG). No se ha determinado el riesgo de complicaciones graves atribuibles a la vacuna antiamarílica en personas infectadas por el VIH.

Las directrices de la OMS para inmunizar a los niños con infección por el VIH y los lactantes nacidos de mujeres infectadas por el VIH difieren muy poco de las directrices generales. Hay que evitar la BCG y la vacuna antiamarílica en los niños infectados por el VIH con síntomas. Sólo se ha dado un caso de complicación grave (neumonía mortal) atribuida a la vacuna antisarampionosa administrada a un adulto gravemente inmunodeprimido. Aunque dos lactantes infectados por el VIH han desarrollado poliomielitis paralítica asociada a la vacuna, son varios millones los niños infectados que han sido vacunados, y no hay ningún indicio de que

corran un mayor riesgo. Los beneficios que reportan las vacunas contra el sarampión y el poliovirus superan ampliamente los riesgos potenciales en los niños infectados por el VIH. La política de administrar sistemáticamente esas vacunas a todos los niños, independientemente de su posible exposición al VIH, ha contribuido de forma muy eficaz al logro de una alta cobertura de inmunización y de control de enfermedades prevenibles. Cualquier cambio de dicha política debería verse precedido de un detenido examen de las posibles repercusiones negativas en los programas de control de esas enfermedades en muchos países.

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