HIV infection and routine childhood immunization: a review

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This review summarizes current experience with immunization of children infected with human immunodeficiency virus (HIV), relevant data on immunization of HIV-infected adults, and in vitro studies with vaccine antigens and HIV-infected cells. Theoretical concerns about the possible effects of repeated antigenic stimulation on the course of HIV infection are also summarized. Finally, available information on the course of vaccine-preventable diseases in HIV-infected children is reviewed. Together these studies provide a current data base for decisions about immunization of HIV-infected children.

The increase in the numbers of children known to be infected with human immunodeficiency virus (HIV) has made it important to provide an appropriate immunization policy for them. The World Health Organization, among others, is therefore concerned about the efficacy and safety of the usual childhood immunizations among this group of children. While the body of knowledge on this subject remains small, there are none the less some significant studies reported in the world literature which provide a scientific basis for such policies. These studies are reviewed below.

VACCINE SAFETY

Increasing awareness of HIV infection in children has led to concern about the efficacy and safety of routine immunizations among HIV-infected children (1, 2). Live vaccines have been contraindicated in children with immunodeficiency diseases because of the potential for disseminated infection with the viral or bacterial vaccine strain (3). Assessment of a similar risk in HIV-infected children is complicated by the fact that it is not always known whether HIV-infected children are actually immunodeficient when immunized. The clinical stage of the disease is referred to where possible in the citations below.

Although inactivated vaccines are not usually considered to present a risk to immunodeficient children, questions have been raised about the potential for any immunization to accelerate the course of HIV infection. Accordingly, the safety of inactivated vaccines must also be considered.

BCG vaccine

Local reactions and disseminated disease have both been described in HIV-infected individuals. In France a 22-year-old man with persistent generalized lymphadenopathy (PGL) developed a local abscess and fistula several days after BCG administration; an acid-fast organism was cultured and the abscess was cleared after 2 months of treatment with isoniazid hydrazide and rifampicin (4). A 29-year-old man with a two-year history of AIDS (acquired immunodeficiency syndrome) was given BCG in Mexico as
intended treatment for AIDS. Four months later he developed fever, followed by a reaction at the site of injection with ulceration and regional lymphadenopathy. Two blood cultures and a culture of the ulcerating lesion grew *Mycobacterium bovis*, BCG strain. He was treated with two drugs for disseminated BCG infection and improved rapidly (5).

In France, 5 HIV-infected infants received Pasteur strain BCG within 2 months of birth and developed local lymphadenitis at 4 to 15 months of age. In all cases, the BCG reaction appeared after clinical symptoms of HIV infection had developed. Four of these infants were treated with antibiotic therapy, three in combination with surgical excision. All five had resolution of adenitis. In one case, the presence of BCG-culture-positive adenitis at a second non-contiguous site suggested dissemination. In a second case, possible dissemination could not be confirmed; local adenitis was accompanied by pneumonitis due to an acid-fast bacillus, but the organism could not be cultured (C. Griscelli & S. Blanche, personal communication, 1987).

The only available data comparing rates of BCG reactions in HIV-seropositive and HIV-seronegative children are from Zaire. In this preliminary survey, rates of local adenitis following BCG immunization were equal in HIV-infected and uninfected children; no dissemination has been observed to date (R. Ryder, personal communication, 1987).

Although the rate of dissemination of BCG in patients with symptomatic HIV infection cannot be determined from these case reports, they raise the possibility of an increased risk for this otherwise unusual complication of BCG immunization.

**Measles vaccine**

Limited data suggest that live measles vaccine does not cause severe complications in children with HIV infection. Seventy-five children with AIDS-related complex (ARC) or AIDS in New York City received one dose of measles, mumps and rubella vaccine (MMR), in most cases, before the diagnosis of HIV infection was made. However, in 23 cases where the children already had clinical symptoms, and even in 5 cases where they already had AIDS, no adverse events were detected in a retrospective chart review. Similarly, no adverse effects were noted among 30 HIV-infected infants who received measles vaccine in Haiti (N. A. Halsey, unpublished data, 1987).

**Polio vaccines**

Reports from the USA and Europe have failed to document adverse reactions to either live oral (OPV) or inactivated (IPV) polio vaccines. The New York City Health Department reviewed outpatient records of 186 children who had received at least one dose of OPV. Most of the children had received OPV before the onset of symptoms, but 46 of them had received a total of 84 doses of the vaccine after the onset of symptoms. No serious adverse effects were recorded. In another report, 23 HIV-infected infants received OPV before HIV infection was suspected, and 3 received IPV; no adverse effects attributable to immunization were noted.

Seventy-one children born to HIV-positive mothers were followed in a joint European study (6). Among the asymptomatic HIV-infected children, 28 were given IPV vaccine and 13 were given OPV vaccine. Among the symptomatic HIV-infected children, 2 were given IPV vaccine and one was given OPV vaccine. No adverse reactions were noted.

There have been no reports of vaccine-associated poliomyelitis among HIV-infected vaccine recipients or their contacts.

**DPT vaccine**

No side-effects were noted in two published reports. In Europe, 56 HIV-positive children (54 asymptomatic and 2 symptomatic) were given diphtheria-pertussis-tetanus (DPT) or diphtheria-tetanus (dT) vaccine without severe adverse reactions (6). In Miami and New York, 171 HIV-infected children were immunized with at least one dose of DPT, and 45% of them completed primary immunization (4 doses); no adverse reactions were noted (2).

**Other vaccines**

One severe reaction has been reported with the use of a live virus vaccine in an adult. A military recruit with asymptomatic HIV infection became symptomatic with cryptococcal meningitis two-and-a-half weeks after smallpox vaccination, and developed disseminated vaccinia infection four weeks after vaccination (7).

Limited studies in both symptomatic and asymptomatic HIV-infected individuals have failed to demonstrate adverse effects from other live and inactivated vaccines. These include: 21 asymptomatic men who received dT, meningococcal and live adenovirus 4 and 7 vaccines; 10 asymptomatic and 25 symptomatic men with persistent generalized lymphadenopathy who received trivalent influenza vaccine and

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23-valent pneumococcal vaccine (8); 29 asymptomatic and 38 symptomatic men with AIDS or ARC who received both bivalent and trivalent influenza vaccine; and 8 asymptomatic children who received hepatitis B vaccine (6).

**IMMUNOGENICITY AND EFFICACY**

Available data on immunogenicity in children and adults show that both primary and secondary antibody responses to immunization are attenuated in the presence of HIV infection, especially when immunodeficiency is present. Vaccine efficacy has been difficult to assess in HIV-infected children from industrialized countries because of the relatively low incidence of both vaccine-preventable disease and HIV infection, and only preliminary studies are available on vaccine efficacy from developing countries.

**Measles**

A study in the USA showed that only 60% of infants with AIDS had measles antibody 5 to 66 months after immunization. However, in Haiti, equal measles seroconversion rates were found among HIV-infected (82%) and uninfected (80%) infants (N. A. Halsey, unpublished data, 1987). A hospital-based study in Zaire provides the only data on efficacy; there was a trend towards lower mortality attributable to measles among HIV-infected children who had previously been immunized, compared with those who had not (0/3 versus 5/13). Responses to polioviruses 1 and 3 were not studied.

In a study of HIV-infected infants who had received 3 doses of IPV before immunodeficiency was apparent, two patterns of response were observed: Among symptomatic infants with normal antigen-induced lymphocyte proliferation (Group I), 8 of 10 had a serological response to 2 or 3 poliovirus antigens. Among symptomatic infants with absent antigen-induced lymphocyte proliferation (Group II), none of 8 had a serological response to any of the 3 poliovirus antigens (9).

**DPT immunization**

Studies on the response to DPT have been reported in persons with various stages of HIV infection. Tetanus toxoid immunization of 21 HIV-infected military recruits (including 20 with lymphadenopathy and 4 with CD4 counts less than 400) produced antibody responses equal to those in uninfected controls. However, only 11 of 21 had a serological response to diphtheria toxoid compared with 18 of 21 controls. Among children with symptomatic infection, several reports have shown a diminished serological response. In 5 paediatric AIDS patients aged 2 to 6 years with a history of at least one previous dose of tetanus toxoid (but without detectable antitoxin levels), repeat immunization with this antigen produced a weak antibody response in two children and no response in the remainder (10).

In a group of children with symptomatic HIV infection who had been immunized with 3 doses of diphtheria and tetanus toxoid after 3 months of age, only 4 of 7 had a serological response to diphtheria and 8 of 13 to tetanus. In the subgroup with absent antigen-induced lymphocyte proliferation, none of 4 had positive tetanus toxoid titres (9). In 15 symptomatic HIV-infected children with a history of three or more doses of DPT, only 9 (60%) had protective levels of tetanus toxoid antibody, and only 3 (20%) had protective levels of diphtheria toxoid antibody compared to 100% of age-matched controls (11). However, as the immunization histories were not documented and the intervals since last immunization were not matched in controls, the conclusions of this study have been criticized (I. M. Onorato et al., unpublished observation, 1987).

Finally an in vitro study of lymphocyte transformation among paediatric patients who had received three or more doses of DPT showed that proliferation rates were 37% to diphtheria toxoid and 48% to tetanus toxoid in children with AIDS-related complex, and zero to both antigens in children with AIDS (12).

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§ See footnote c.

‖ See footnote d.
Other vaccines

Although one study showed equivalent short-term antibody responses to influenza and pneumococcal vaccine in healthy controls and both symptomatic and asymptomatic HIV-infected men (8), other studies have shown a suboptimal antibody response among HIV-infected cohorts, including 14-valent pneumococcal vaccine in men with ARC, AIDS or no symptoms (13), 23-valent pneumococcal vaccine and trivalent influenza vaccine in adult haemophiliacs with AIDS and ARC (14), meningococcal and live adenovirus vaccines in asymptomatic men, and hepatitis B vaccine in men with persistent generalized lymphadenopathy or no symptoms (15).

Even when the initial antibody response to immunization has been adequate, the antibody may decline to unprotective levels as the HIV infection produces further immunosuppression. In a study of homosexual men with naturally acquired immunity to hepatitis B, HIV-seropositive immuno-suppressed subjects were significantly more likely than HIV seronegative subjects to have lost anti-HBS antibody after a three-year follow-up (16).

Routine immunization and the course of HIV infection

Activation of HIV-infected lymphocytes in vitro leads to HIV expression followed by cell death, suggesting that repeated antigenic stimulation by infectious agents may shorten the latency period in AIDS (17). This theory is supported by an epidemiological study which shows that both homosexual men in the USA with AIDS and African heterosexuals with AIDS have a higher prevalence of antibodies to various infectious diseases than healthy controls in the USA (18). Concern about the role of infectious disease antigens has been extended to concern about the possible role of vaccine antigens in shortening the HIV latency period (2).

While an in vitro study demonstrated that HIV infection of T cells was amplified after activation by tetanus toxoid (19), data from prospective human studies have failed to show any adverse effects of immunization on immune function or progression of symptoms among HIV-infected recipients of vaccines. However, these studies have limited follow-up and do not compare immunized subjects with controls. For example, in a study of HIV-infected men, 10 with no symptoms and 25 with persistent generalized lymphadenopathy received both trivalent influenza vaccine and 23-valent pneumococcal vaccine. There was no change in T-cell counts or evidence of clinical deterioration after 4 to 6 weeks of follow-up. Nelson followed the levels of p24 antigen, a marker of viral antigenaemia, and found that four weeks after immunizing 67 HIV-infected men with monovalent influenza vaccine, only one subject had an increase in p24 level. In addition, available data indicate that several hundred seropositive military recruits must have received multiple immunizations without ill effect before routine screening and exclusion of HIV-seropositive applicants were introduced (20, 21). A single case report with short-term follow-up describes repeated IPV immunization in a physician with AIDS, and speculates that this procedure may have produced beneficial immune amplification (22).

Vaccine-preventable diseases in HIV-infected children

Decisions about whether to continue to immunize HIV-infected infants with a given antigen should also be influenced by data on the observed incidence and severity of the target diseases in HIV-infected children. In the USA there have been 5 reported cases of measles in children with HIV infection, including 4 in symptomatic children (2 AIDS, 2 ARC), and one in an asymptomatic child. The two children with AIDS both died with measles; these were the first measles deaths in the USA since 1983.

Among hospitalized children with measles in Zaire, mortality was the same in the 16 HIV-infected (31%) as in the 298 uninfected children (28%). This study cannot be extrapolated to overall measles mortality in Zaire since it is possible that a higher proportion of HIV-infected measles cases may have required hospitalization.

Studies of tuberculosis among adults in the USA and Zaire suggest an increased rate of overt disease in HIV-infected patients (23). One case of disseminated pertussis has been reported in a child with AIDS. Data are not available on the incidence or course of poliomyelitis, diphtheria or tetanus among HIV-infected individuals. However, the experience with other infectious diseases in children with AIDS (24) and the well-known defects in both humoral and cellular immunity in these children (2) would

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\(^1\) DOUGLAS, J. M. ET AL. Response to pneumococcal and influenza vaccines in gay men with asymptomatic HTLV-III infection and with AIDS. Paper presented at the 26th Interscience Conference on Antimicrobial Agents and Chemotherapy, 28 September–1 October 1986, New Orleans, LA, USA

\(^2\) See footnote d.

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\(^3\) See footnote e.

\(^4\) See footnote b.

\(^5\) See footnote g.


predict increased rates of morbidity and mortality to vaccine-preventable diseases.

**DISCUSSION**

The documented reactions to some live vaccines and the diminished immunogenicity of both live and killed vaccines must be balanced against the risks and known consequences of natural infection with the antigens in question. Experience with inactivated vaccines in HIV-infected children suggests that these antigens are generally free from major side-effects in the short term. Insufficient data are available to judge whether minor or local reactions are increased in this population, and there have been no studies to examine the neurological reactions to pertussis vaccine among HIV-infected children. The serological response to inactivated vaccines in HIV-infected children is clearly diminished compared with normal children, and is related to the degree of immunodeficiency.

With live viral and bacterial vaccines, there is a theoretical basis for concern about serious side-effects in HIV-infected children. Severe reactions have already been documented in isolated instances to BCG and smallpox vaccine. However, denominators for these events are not available, and there have been no documented severe reactions to measles or polio vaccines. The serological response to all live vaccines is probably diminished when immunodeficiency has developed. The theoretical risk of accelerating HIV infection by immunization is not supported by limited clinical information, and may be trivial in contrast to other natural sources of antigenic stimulation, especially in areas of the world with high levels of endemic infectious diseases.

This review provides general support for the recommendations on immunization of HIV-infected children that were developed by the World Health Organization (1)\(^a\),\(^b\) and by the Advisory Committee on Immunization Practices (ACIP) of the United States Public Health Service (2). For asymptomatic HIV-infected children both groups recommend continued administration of standard vaccines. For symptomatic HIV-infected children (e.g., AIDS, ARC) both groups recommend continued administration of inactivated vaccines, but differ in their recommendations on live vaccines. The ACIP recommends against the use of any live vaccines (OPV, MMR, BCG) in this group, and suggests substitution of IPV for OPV. The World Health Organization recommends against the use of BCG in symptomatic HIV-infected children but advises continued administration of measles and OPV vaccines in asymptomatic HIV-infected children.

Where the incidence of poliomyelitis and measles is low, as in the USA, withholding live vaccines may be considered, at least until further data on their safety is obtained. However, the two measles fatalities which have occurred in AIDS patients in the USA suggest that measles immunization should be provided to susceptible children with symptomatic HIV infection unless the risk of exposure to measles can be eliminated.

In areas of the world where the incidence of poliomyelitis and measles remains high the current lack of evidence of side-effects to live measles and OPV vaccine supports the WHO policy of continued administration of both vaccines to symptomatic HIV-infected children. Inactivated polio vaccine can be used as an alternative to live vaccine.

More information is needed before considering the recommendations on the use of BCG in HIV-infected children. Avoiding immunization with BCG in symptomatic children is still appropriate,\(^b\) since efficacy would probably be minimal in this group, and the risk of dissemination has been reported. Prospective studies should be initiated, or ongoing studies modified, to collect data on the risks and benefits of BCG vaccination in HIV-infected asymptomatic children. If possible, studies should compare different BCG strains.

Prospective multicentre studies of the safety and efficacy of other routine vaccines in HIV-infected children are also required and should be initiated promptly.

**ACKNOWLEDGEMENTS**

This article is based on one that was published by the same authors in the *Lancet*. 2: 669–672 (1987).
L'intérêt que suscite l'infection par le VIH chez l'enfant a conduit à se poser des questions quant à l'innocuité et l'efficacité des vaccinations systématiques chez les enfants infectés par le VIH. Cet article passe en revue les données actuelles relatives à la vaccination d'enfants infectés par le VIH, les données pertinentes concernant la vaccination d'adultes infectés par le VIH et les résultats d'études in vitro où sont mis en présence des antigènes vaccinaux et des cellules infectées par le VIH. Le problème théorique des effets d'une stimulation antigénique répétée sur l'évolution de l'infection par le VIH, et les données dont on dispose pour l'évolution, chez des enfants infectés par le VIH, des maladies évitables par la vaccination, sont également examinés. Les résultats de toutes ces études constituent un ensemble de données permettant d'appuyer la décision de vacciner ou non un enfant infecté par le VIH.

Les réactions atténuées à certains vaccins vivants et l'immunogénicité réduite des vaccins vivants comme des vaccins tués chez ces sujets doivent être pesées face aux risques et conséquences connus de l'infection naturelle par les antigènes concernés. L'expérience que l'on a de l'administration de vaccins inactivés à des enfants infectés par le VIH laisse à penser que ces antigènes sont généralement dépourvus d'effets secondaires graves à court terme. Chez ces enfants, la réponse sérologique aux vaccins inactivés est nettement plus faible que chez les enfants normaux, et est liée au degré d'immunodéficience. Les vaccins viraux et bactériens vivants risquent théoriquement d'entrainer des effets secondaires graves chez les enfants infectés par le VIH. On a déjà observé de telles réactions isolées après une vaccination BCG ou antivariolique. Toutefois, on ne connaît pas les dénominateurs de ces accidents et aucune réaction grave n'a été observée avec le vaccin antirougeoleux ou antipoliomyélitique. La réponse sérologique à l'ensemble des vaccins vivants est probablement réduite une fois l'immunodéficience installée.

Cet article appuie totalement les recommandations de l'Organisation mondiale de la Santé au sujet de la vaccination des enfants infectés par le VIH, comme par exemple la poursuite de l'administration des vaccins classiques chez les enfants présentant une infection asymptomatique par le VIH. L'OMS déconseille en revanche l'emploi du BCG chez les enfants atteints d'une infection symptomatique par le VIH, tout en conseillant la poursuite de l'administration des vaccins antirougeoleux et antipoliomyélitique buccal chez ces mêmes enfants.

Il faudra avoir davantage de données avant de reconsidérer les recommandations sur l'emploi du BCG chez les enfants infectés par le VIH. On peut continuer à éviter de vacciner les enfants symptomatiques par le BCG, car l'efficacité de cette vaccination sera probablement négligeable dans ce groupe et il existe un risque de généralisation de l'infection tuberculeuse. On devra entreprendre des études prospectives, ou modifier les études en cours, afin de recueillir des données sur les risques et les avantages de la vaccination par le BCG chez les enfants présentant une infection symptomatique par le VIH, en comparant si possible différentes souches de BCG.

Des études multicentriques prospectives sur l'innocuité et l'efficacité, chez les enfants infectés par le VIH, des autres vaccins administrés en routine, sont également nécessaires et devront débuter sans tarder.

REFERENCES


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