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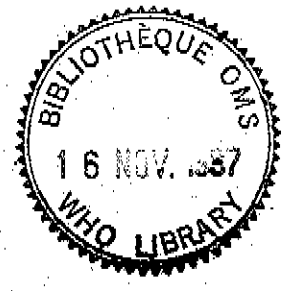
REPORT ON WHO CONSULTATION ON HIV AND ROUTINE CHILDHOOD IMMUNIZATION

GENEVA
12-13 AUGUST 1987



WORLD HEALTH ORGANIZATION

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1. Introduction

The widespread epidemic of infections due to Human Immunodeficiency Virus (HIV) and related viruses and the resultant immune deficiency disorder known as AIDS have given cause for concern regarding the administration of vaccines in the Expanded Programme on Immunization (EPI). A consultation was jointly sponsored by the World Health Organization Special Programme on AIDS and the EPI to review available information on HIV infection and immunization in order to assess the need for modification of the guidelines established in 1986 by the Global Advisory Group of the EPI. The meeting was held in Geneva on 12-13 August 1987. Thirteen participants from eight countries attended the meeting, including immunologists, virologists, disease control specialists, infectious disease specialists and experts in immunization and epidemiology.

Professor F.K. Nkrumah (Zimbabwe) chaired the meeting, Dr R. Ryder (USA/Zaire) and Professor Wasz-Höckert (Finland) presided over working groups and Dr N. Halsey (USA), Dr D.W. Mulder (Netherlands) and Dr I. Onorato (USA), served as rapporteurs.

2. Objectives

The objectives of the WHO consultation on HIV and Routine Childhood Immunization were:

(i) to review the current worldwide epidemiology of HIV infection and the natural history of HIV infection in children;

(ii) to review the epidemiology of the six target diseases for EPI and available information on the clinical manifestations of the target diseases in children with HIV infection;

(iii) to review the available data on safety, immunogenicity and efficacy of the six EPI vaccines in children with HIV infection;

(iv) to review available information on the potential for live and inactivated vaccines to accelerate the course of HIV infection in infected individuals;

(v) to propose revisions to the existing EPI guidelines, if indicated, for consideration by the EPI Global Advisory Group; and

(vi) to propose additional studies to address unanswered questions about HIV infection and immunization.

3. Current status of AIDS in children

As of 11 August 1987, 122 countries had reported a total of 56 395 cases of AIDS to WHO. The increasing seroprevalence rates for HIV infection and the natural history of HIV infection suggest that the current worldwide epidemic will result in increasing numbers of AIDS cases in most countries for several years irrespective of the effectiveness of HIV prevention programmes.

The total number of paediatric AIDS cases is not known, but represents 1.4% of reported cases in the United States and may represent as many as 3% of cases in developing countries. This figure may underestimate the problem due to unrecognized infant deaths from AIDS and the difficulty in diagnosing AIDS in children, especially in countries where malnutrition, chronic diarrhoea and respiratory diseases are common, and where serological testing for HIV is not readily available.

Infants and children mainly acquire HIV infections from maternal-infant transmission and from parenteral exposures (transfusion of infected blood and blood products, and exposure to non-sterile needles/syringes or other skin-piercing instruments). The risk of an infant acquiring HIV infection

from a seropositive mother has been estimated to be 25% to 50%. In countries where heterosexual transmission of AIDS is the predominant mode of spread, paediatric cases represent a higher percentage of the total number of reported cases than in areas where sexual transmission of HIV primarily involves male homosexuals and bisexuals.

None of the currently available serological tests has proven to be reliable for accurately determining the presence of HIV infection during infancy since: (1) passively acquired maternal antibodies may persist until 12 months of age or longer, and (2) some infected infants lack detectable antibody.

Longitudinal studies in developing countries indicate that approximately 15% to 26% of perinatally infected infants die in the first nine months of life. The cumulative risk of dying from HIV infection is not known but most experts predict that the majority of infected infants will die from HIV-related disease. Insufficient data are available in most countries to assess accurately the impact of HIV infections on overall child survival rates. In countries with high rates of seropositivity in women of childbearing age, it is expected that HIV infections will contribute importantly to overall infant and child mortality.

4. The epidemiology of EPI target diseases and the impact of immunization

Implementation of the EPI has resulted in marked improvements in immunization coverage in developing countries. In 1974 less than 5% of infants in such areas had received three or more doses of DPT and poliomyelitis vaccine. In 1987, it is estimated that 50% of infants in these areas have received three or more doses of these vaccines. Current coverage rates for BCG and measles vaccine are estimated at 45-50%. All EPI antigens effectively prevent severe disease and mortality from the target diseases. It is estimated that the use of these vaccines in developing countries is now preventing over a million deaths per year from measles, neonatal tetanus and pertussis and over 175 000 cases of poliomyelitis. Nevertheless, over 3 million deaths still occur annually from the first three diseases as well as some 250 000 cases of poliomyelitis.

Intensive efforts are under way to expand immunization coverage throughout the world so that all children will benefit from the prevention of these diseases.

5. EPI target diseases in HIV-infected individuals

5.1 Measles

Several cases of measles have been reported in unvaccinated HIV-infected children in the United States, with two deaths; these are the first reported deaths from measles in the United States since 1983. As in other patients with severe, cell-mediated immunodeficiency disorders, progressive pneumonitis was a predominant feature in most of these cases. One patient did not have a rash. These observations suggest that atypical clinical presentations may also be more frequent among HIV-infected individuals. Based upon the limited number of cases observed, the risk of death from measles in HIV-infected persons appears much higher than the 0.1% mortality rate observed in measles cases without HIV infection in the United States during recent years.

An investigation of 314 children hospitalized with measles in Zaire showed similar overall case fatality rates for HIV-infected and uninfected children, although the mortality rate for children over nine months of age was higher among HIV-infected than uninfected children (50% versus 29%). Although the number of observed cases is small, measles in HIV-infected infants and children appears more severe than in HIV-negative children.

5.2 Other target diseases

At this time no confirmed cases of poliomyelitis, tetanus or diphtheria occurring in HIV-seropositive individuals have been reported. Several cases of pertussis have been observed among HIV-seropositive persons in the United States with at least one death. Tuberculosis and disease caused by other mycobacteria (especially Mycobacterium avium intracellulare) have been recognised as common complications in patients with AIDS throughout the world. In most instances, disease is the result of endogenous reactivation in patients exposed to the microorganism prior to the onset of HIV-related immune deficiency. Insufficient data are available on tuberculosis following primary exposure to M. tuberculosis in HIV-infected infants and children to determine the severity of disease.

6. Vaccination of infants born to HIV-infected mothers and of children with confirmed HIV infections

6.1 Measles vaccine

Seroconversion studies have been performed on only a limited number of HIV-infected infants. The few HIV-infected infants who were evaluated prospectively did seroconvert following measles immunization.

A study in 45 seropositive Haitian infants under 12 months of age born to seropositive women revealed seroconversion rates to measles vaccine equivalent to age-matched infants born to seronegative women. A follow-up study of this population revealed that measles vaccination was highly correlated with survival from 9 through 39 months of age. Serological testing 5 months to 5 years after vaccination of infants who had acquired HIV infections at birth revealed that only 6 of 10 had detectable measles antibodies. No complications were observed in separate studies of over 70 HIV-infected infants in the United States who had received measles vaccine, including infants who had onset of HIV-related disease prior to immunization.

6.2 Oral poliomyelitis vaccine (OPV)

Patients with primary immunodeficiency disorders have an increased risk of paralytic complications (estimated 5/1000) following OPV. However, more than 180 HIV-infected infants in the United States have received OPV without apparent complications, and no complications from OPV have been reported to WHO or were known to the meeting participants. One study of HIV-infected infants who received OPV prior to onset of immunodeficiency showed a 90% serological response to poliovirus type 2.

6.3 DPT

In the United States, more than 200 HIV-infected infants have received one or more doses of DPT, and no unusual adverse effects have been reported. Serological studies in a small number of infants with HIV infections revealed some diminished or absent responses to diphtheria and tetanus toxoids.

6.4 BCG

WHO is aware of 10 HIV-infected infants (5 France, 5 Africa) who developed regional lymphadenitis secondary to BCG vaccination. These infants had acquired their HIV infections perinatally from their mothers or from transfusions at the time of birth.

BCG vaccine was administered from birth to 2 months of age and the lymphadenitis developed at 4 to 15 months of age, and always after the onset of HIV-related symptomatology. Several patients developed fluctuance and/or fistulous drainage requiring surgical intervention. Several patients responded to chemotherapy alone. BCG was also isolated from a non-contiguous (inguinal) lymph node in one patient, suggesting dissemination.

The onset of regional lymphadenitis appearing after the onset of HIV-associated symptoms suggests reactivation of persisting BCG organisms in lymph nodes. The total number of HIV-infected infants who have been immunized is unknown and it is not known whether the rates of complications in HIV-infected infants differ from expected rates in HIV-negative infants. A study of 185 HIV-infected infants who received BCG in Zimbabwe revealed five cases of regional lymphadenitis (noted above). The rate of regional lymphadenitis after BCG in these infants (27 per 1000) was not significantly different from the rate noted for the entire city (15-19 per 1000). Preliminary results from a study in Kinshasa showed equal rates of lymphadenitis following BCG administration among HIV-infected and uninfected children.

7. Immunization of HIV-infected adults

The serological response to immunization with various antigens (e.g., pneumococcal, influenza, diphtheria, hepatitis B) in HIV-infected adults is generally diminished and is inversely correlated with the presence and severity of HIV-related disease. The response to tetanus toxoid was normal in one study of HIV-seropositive military recruits.

Two additional instances of progressive local ulcers and regional lymphadenitis have been reported in 22- and 29-year-old symptomatic HIV-infected individuals in France and Mexico. The patient vaccinated in Mexico had AIDS at the time of vaccination and also had two positive blood cultures indicating dissemination of BCG. Both patients responded to anti-tuberculous chemotherapy.

One asymptomatic HIV-infected military recruit in the United States developed disseminated vaccinia and clinical AIDS after receiving smallpox vaccine and multiple other antigens as part of a routine immunization programme. The total number of HIV-seropositive recipients of smallpox vaccine is not known.

8. The effect of immunizations and naturally occurring infections on HIV infections and clinical course

Several laboratory investigations have determined that the CD4 (helper) lymphocytes grown in tissue culture have increased susceptibility to HIV virus infection. In addition, the virus grows to higher titres in activated cells, and HIV-infected lymphocytes are more susceptible to cell death after activation. The normal immune response following immunization includes the stimulation of lymphocytes. The single case of progression to AIDS after receiving multiple immunizations noted above raised the question of whether administering multiple immunizations might increase the rate of progression of HIV-related disease. However, the administration of multiple live viral vaccines (including poliomyelitis, adenovirus, measles, mumps and rubella) to 21 asymptomatic HIV-seropositive adults did not result in any change in clinical status. Similarly, 105 seropositive individuals who received a 24-valent pneumococcal vaccine and four different influenza vaccines did not manifest any changes in serum levels of an antigen (p24) produced by HIV. Finally, in a study of 210 HIV-infected children in New York City, the number of antigens received at 6 and 12 months of age was the same for children who later developed symptomatic infection, AIDS, or remained asymptomatic.

Controlled trials of withholding routine immunizations from HIV-infected children to evaluate the effect of immunization on HIV disease course have not been conducted and would be unethical in the opinion of the meeting participants. The available clinical data do not support the hypothesis that immunizations alter the course of HIV infections. Laboratory studies of infants and adults in developing countries have indicated that they are in a constant state of immune stimulation due to multiple acute and chronic infections. The added antigenic stimulation from immunization is likely to be trivial in contrast to other natural sources of antigenic stimulation, and to stimulation from infection with the disease the vaccines prevent.

9. Risk/benefit evaluations

The consultation evaluated the limited information regarding safety and efficacy of immunizations in HIV-infected individuals. Immune deficiency complicates evaluation of response to immunization. Immunodeficient individuals are at increased risk of developing severe complications from naturally-occurring disease (e.g., high rates of active tuberculosis and probable increased severity of measles in persons with HIV infections).

Although the risks from live vaccines may be increased in immunodeficient children, this risk is almost always lower than the risk from more virulent wild-type organisms. Therefore, when the risk of exposure to wild-type organisms is high, as occurs in most developing countries, it appears far safer to administer vaccines than to allow natural infections to occur.

In immunodeficient individuals, the host response and resulting immunity following immunization may be diminished. This is evidenced by the variable responses observed in HIV-infected individuals. Available evidence supports immunizing HIV-infected individuals as early in life as possible before the progression of symptomatic immunodeficiency, in order to maximize the host responsiveness and minimize potential risks.

The consultation considered the suggestion of serological screening for HIV prior to administering vaccines. This suggestion was rejected as impractical and potentially misleading, especially for infants. Although all infants born to HIV-seropositive women will initially have serum antibodies to HIV, only 25% to 50% will be HIV-infected. It would be inappropriate to withhold vaccines of known benefit from the 50% to 75% of uninfected infants because of theoretical concerns regarding the safety of these vaccines.

After consideration of the available data, the consultation agreed on the following CONSENSUS STATEMENT:

Concern has been raised that children infected with the human immunodeficiency virus (HIV) who receive routine childhood immunizations may have decreased immune responses and be at increased risk for adverse effects or acceleration of HIV-induced immunosuppression. Limited experience suggests that the likelihood of successful immunization is reduced in some HIV-infected individuals but that the risk of serious adverse effects remains low. The theoretical risk of accelerating HIV infection by simultaneous administration of multiple antigens is not supported by limited clinical information and is likely to be negligible in contrast to other natural sources of antigenic stimulation.

Having reviewed the available information in Geneva on 12 and 13 August 1987, the WHO informal consultation on HIV and routine childhood immunization:

1. Endorses the 1986 Expanded Programme on Immunization (EPI) Global Advisory Group recommendations on the use of EPI antigens:

> "In countries where human immunodeficiency virus (HIV) infection is considered a problem, individuals should be immunized with the EPI antigens according to standard schedules. This also applies to individuals with asymptomatic HIV infection. Unimmunized individuals with clinical (symptomatic) AIDS in countries where the EPI target diseases remain serious risks should not receive BCG, but should receive the other vaccines (Table)."

TABLE

Recommendations on the use of EPI antigens in HIV-infected individuals in countries where the EPI target diseases remain important causes of morbidity

	Vaccine	Asymptomatic	Clinical AIDS
Infants	BCG	Yes	No
	DTP	Yes	Yes
	OPV	Yes	Yes
	IPV	Yes	Yes
	Measles	Yes	Yes
Women	Tetanus toxoid	Yes	Yes

2. In accordance with the Global Advisory Group, notes that live vaccines are not usually given to immunocompromised individuals, but agrees that, in areas where the risk of exposure to measles and poliovirus is high, the benefits of immunization outweigh the apparently low risk of adverse effects from these vaccines, even in the presence of symptomatic HIV infection. Inactivated poliomyelitis vaccine (IPV) is an alternative to OPV for immunization of children with symptomatic HIV infection who may be at increased risk of OPV-associated paralytic poliomyelitis;

3. Notes that although a theoretical risk exists, evidence for an increased rate of adverse reactions after BCG immunization among asymptomatic HIV-infected individuals remains inconclusive. Therefore,

   (a) for asymptomatic HIV-infected individuals:

   - 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 a limited number of areas, the risk of tuberculosis is low, but BCG is recommended as a routine immunization, in these areas BCG may be withheld from individuals known or suspected to be infected with HIV;

   (b) for symptomatic HIV-infected individuals, BCG should be withheld;

4. Emphasizes the EPI recommendation to immunize children as early in life as possible. Vaccine-associated adverse effects may be minimized and vaccine response optimized by beginning immunization before the progression of HIV-induced immunosuppression;

5. Endorses the simultaneous administration of multiple antigens such as BCG, DTP, polio and measles vaccines when indicated;

6. Strongly encourages further investigations in the following areas:

   (a) Safety of immunizations in HIV-infected children:

   (i) Surveillance of HIV-infected children to permit rapid identification of any unexpectedly frequent adverse events following immunization;

   (ii) Establishment or modification of population-based surveillance systems to detect rare serious adverse events associated with immunization of HIV-infected children;

(iii) Comparison of the rates of frequent and less severe adverse events which occur in HIV-infected and uninfected children following immunization.

(b) The natural history of vaccine-preventable diseases in HIV-infected children.

(i) Determination of the rates of serious complications of vaccine-preventable diseases in HIV-infected children in health care facilities and in the community, and correlation of such complications with the stage of HIV infection and degree of immunosuppression;

(ii) Establishment or modification of population-based surveillance systems to detect serious complications of vaccine-preventable diseases in HIV-infected children;

(iii) Assessment of the role of immune globulin in protection of HIV-infected children against vaccine-preventable diseases.

(c) Immunogenicity and efficacy of immunization in HIV-infected children.

(i) Determination of the serological response to immunization in HIV-infected children compared to uninfected children and correlation of vaccine response to the stage of HIV infection and the degree of immunosuppression;

(ii) Development of methods to improve vaccine responses of HIV-infected children, if these are found to be decreased;

(iii) Determination of the persistence of vaccine-induced antibody;

(iv) Prospective follow-up of immunized HIV-infected children and retrospective evaluation of cases of vaccine-preventable diseases to determine rates of vaccine failure in HIV-infected children.

(d) Possible activation or acceleration of HIV infection by repeated antigenic stimulation with immunizations, including simultaneous administration of multiple antigens.

(i) Detection of increased HIV replication following immunization of HIV-infected children;

(ii) Detection of immunological abnormalities following immunization of HIV-infected children;

(iii) Retrospective studies of the relationship between the total number of immunizations received and/or number of antigens received simultaneously by HIV-infected children and the onset of symptomatic HIV infection, progression of clinical HIV disease and/or fatal outcome of HIV infection. The informal consultation agreed that prospective placebo-controlled double-blind studies in which some HIV-infected children would not receive recommended immunizations are not appropriate.

(e) The immunogenicity and efficacy of tetanus toxoid immunization of HIV-infected pregnant women in the prevention of neonatal tetanus.

ANNEX

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