WHO/GPA/SFI/89.2
Original: English
Distr.: General

GLOBAL
PROGRAMME
ON AIDS

REPORT ON THE MEETING OF THE TECHNICAL WORKING GROUP ON HIV/AIDS IN CHILDHOOD

GENEVA
27 FEBRUARY – 1 MARCH 1989

WORLD
HEALTH
ORGANIZATION

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ORGANISATION MONDIALE DE LA SANTE

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CONTENTS

1. INTRODUCTION

Although the acquired immunodeficiency syndrome (AIDS) was first described in adults, it has become evident over the past few years that the human immunodeficiency virus (HIV) pandemic is already a major cause of infant and childhood mortality in certain regions of the world. Most paediatric AIDS is the result of transmission from an infected woman to her fetus or infant; thus areas with a high prevalence of HIV infection in women have been the areas most affected. Frequently the child is the index AIDS case in a family.

The meeting was opened by Dr J. Chin, Chief, Surveillance, Forecasting and Impact Assessment Unit, WHO Global Programme on AIDS. Dr N. Agata was appointed Chairman, Dr M. Oxtoby and Dr J. Ziegler Rapporteurs.

The group was convened to review the available information on the transmission, natural history, diagnosis, and surveillance of HIV/AIDS in childhood, in order:

(1) to define and allot priorities to unresolved questions with respect to HIV infection in infancy and childhood; and

(2) to evaluate existing paediatric AIDS case definitions and suggest approaches for improving childhood HIV/AIDS surveillance.

Several areas of importance in paediatric AIDS were not addressed in depth at this meeting and are therefore not included in this report. They are: psychosocial and behavioural research, therapeutics, adolescent infection, and issues related to HIV and childhood immunization. Transmission and natural history issues were discussed in a public health setting rather than from the perspective of basic science or clinical practice. Thus the recommendations in this report are not intended to cover all research needs related to HIV infection in children, but rather those of highest priority for surveillance and epidemiological research.

The WHO estimates of HIV/AIDS were presented as a framework for the working group. It is estimated that at least 1.5 million women throughout the world are infected with HIV. Most are believed to be in sub-Saharan Africa and the Caribbean area, where heterosexual transmission is the primary mode of HIV transmission. A model for estimating the number of AIDS cases in children in Africa has been developed by WHO, based on findings from seroprevalence studies in pregnant women and on the assumptions that: (a) these HIV-infected women aged 15-49 years have a live birth on average every three years, (b) the transmission rate from an infected woman to her fetus or infant averages about 25%, and (c) approximately 80% of infected children will die by the age of 5 years as a result of their HIV infection. Based on these assumptions, in sub-Saharan Africa alone the cumulative number of HIV-infected infants was estimated to have been close to 80 000 by the end of 1987.

2. EXISTING DATA AND CURRENT STUDIES

2.1 Transmission, natural history, and diagnosis of HIV infection

2.1.1 Transmission from an infected woman to her fetus or infant

Reflecting patterns of heterosexual transmission, HIV infection may already be responsible for large increases in childhood, and particularly infant, mortality. However, there is a paucity of data on (a) the frequency with which HIV passes from an infected woman to her fetus or infant, (b) the stage(s) in the reproductive process at which such events take place, (c) the factors present in the mother that increase or decrease the risk of infection of her fetus or infant, and (d) the likely mechanism(s) for such a process. The data do not so far suggest that any form of transmission exists that does not involve transmission from an infected woman to her fetus or infant, exposure to contaminated blood, sexual contact or, in rare instances, breast-feeding.

The frequency with which maternal infection results in transmission of HIV before, during, or shortly after birth is thought to range between 10% and 50%. There is some limited evidence to suggest that the risk of transmission is highest at the time of maternal viraemia shortly after her infection has occurred. The risk may increase again when the mother's infection progresses and she becomes antigenaemic and immunodeficient. Little is known of other maternal factors that may influence transmission rates. There is evidence that fetal infection can take place as early as at the twelfth to fifteenth week of gestation. It is not known what proportion of infants destined to be infected are already infected at this stage, and in what proportion infection occurs late in pregnancy or during the birth process. There is limited evidence implicating breast-feeding as a mode of transmission; it appears to be important when maternal seroconversion takes place during lactation, but the available data indicate that the additional risk from breast-feeding for a child already exposed during pregnancy and delivery is small compared with the risk from the other prior exposures. In most situations, therefore, the advantages of breast-feeding outweigh the potential small additional risk of HIV transmission from breast-feeding.

2.1.2 Diagnostic tests for HIV infection in infancy

The available data regarding transmission from an HIV-infected woman to her fetus or infant are limited. This can be attributed in large part to the difficulty of diagnosing HIV infection in infancy. The diagnosis in adults is dependent on the detection of antibody to HIV, which is principally of the IgG class. Since IgG crosses the placenta, the presence of maternal IgG antibody interferes with the diagnosis of HIV infection in infants. Maternally derived antibody usually becomes non-detectable within 6-9 months in the majority of uninfected infants. It has, however, been found to persist for up to 18 months in some children in European studies, and up to 12 months in African studies. A substantial proportion, probably over 20%, of infected children will die of HIV-related disease before the age of one year. Thus early diagnosis of HIV infection is a matter of high priority. Experimental tests of potential future value include the following.

(a) Polymerase chain reaction (PCR). This can be used to detect small numbers of copies of various HIV genes incorporated into the deoxy-ribonucleic acid (DNA) of infected cells and can also detect HIV messenger ribonucleic acid (mRNA), indicating viral proliferation. Among the problems are false positive reactions and the technical complexity of the test. Standardization is required to ensure the comparability of data from different laboratories, and allowance must be made for possible regional strain variations. The technique can detect proviral DNA, which may not always imply true active infection.

(b) Virus culture. Although virus culture has been considered the model for the evaluation of other techniques, the sensitivity of this method for the diagnosis of HIV infection ranges widely between laboratories. In general, it is thought to be less than 100%.

(c) HIV-specific IgM. IgM antibody does not cross the placenta and is produced early in infection. The detection of infection-specific IgM is routinely used to diagnose other congenital infections where maternal antibody in infant blood interferes with conventional tests. Attempts to develop tests detecting HIV-specific IgM antibody have met with sensitivity and specificity problems. Nor is it clear whether HIV-specific IgM antibody is regularly produced by HIV-infected infants or not.

(d) HIV-specific IgA. Since these antibodies do not cross the placenta, an HIV-specific IgA test may have diagnostic value. It remains to be fully evaluated.

(e) HIV antigens. This method may be of value in diagnosing HIV infection in sick infants of HIV-seropositive mothers, since the antigen levels are known to increase with increasing immunosuppression. Here too the sensitivity of the test remains to be fully evaluated.

(f) IVAP (*in vitro* antibody production). The detection of HIV antibody-producing cells in the infant's blood may be a reliable method of early diagnosis of HIV infection. Careful evaluation of its sensitivity and specificity is necessary.

The development of simplified or rapid methods of testing for serological markers of HIV infection for use in public health should continue to be encouraged. Such methods could include among others latex agglutination assays for HIV antibody, and the use of filter-paper dried blood specimens.

2.1.3 Pregnancy and HIV infection

The impact of the HIV/AIDS epidemic on infants and children is not necessarily limited to the direct effects of HIV infection. The effect of maternal HIV infection on the outcome of pregnancy can be assumed to be due both directly to the effect of the infection on maternal health and indirectly to the social and economic impact of the infection on the family. In addition, maternal illness will affect the mother's ability to care for her children after birth as well as the likelihood of her carrying other pregnancies to term.

The altered immune function of pregnancy might be anticipated to lead to acceleration of HIV-related disease in pregnant women. The initial impression that pregnancy was detrimental to infected women was probably due at least in part to selection bias since prior to the availability of tests for the serological markers of HIV infection, only those with symptomatic HIV infection could be diagnosed.

2.1.4 Natural history of HIV infection in children

The overall outcome for HIV infection in the newborn is still not clear. It has been well documented that many infected infants die as a result of HIV-related disease in the first year of life. In other HIV-infected children a prolonged period of relative freedom from symptoms (perhaps some years) is followed by the development of disease, a pattern that is probably similar to the natural history of HIV infection in adults. This has important implications for health care systems as well as for individual families, since it will result in increased numbers of older children in need of care for prolonged periods.

2.2 Surveillance, forecasting, and impact assessment

2.2.1 Surveillance approaches

Development of the ability to assess the impact of HIV-related disease in children from different geographical regions, and over time, is an essential part of the response to this global pandemic. No single approach is sufficient, and several complementary approaches are being used. One broad approach to assessing the impact of HIV in children is based on combining data on the prevalence of HIV among women of childbearing age with data and estimates on the rate of transmission from mother to infant and the observed natural history of HIV infection in children. Another approach consists of analysing trends in overall and cause-specific mortality rates in relation to HIV seroprevalence levels in different populations. A third approach is surveillance of AIDS cases; the reporting of individual AIDS cases to public health authorities is an important part of HIV surveillance, as it is for other communicable diseases.

The development and the use of an adequate case definition for AIDS are central to these efforts. Any definition of AIDS for surveillance purposes creates of necessity an arbitrary cut-off point in the whole spectrum of HIV-related disease from "non-AIDS" to "AIDS". In developing case definitions, conflicting objectives must be balanced. As far as possible the definition should include most children with significant HIV-related disease and exclude uninfected children. It should be as simple as possible, given the diverse manifestations of HIV-related disease. Lastly, it should be as universal as possible, while allowing for major differences in diagnostic practices.

2.2.2 AIDS case definition

(a) Difficulties in developing paediatric AIDS case definitions

(1) The spectrum of disease and the natural history of HIV infection are less well described in children than in adults.

(2) Indicator diseases seen in immunocompromised HIV-infected children overlap with diseases commonly seen in children not infected with HIV.

(3) The persistence of maternal antibody in an uninfected child's serum, sometimes for up to 12 or even 18 months of age, complicates the diagnosis of HIV infection. Conversely, some HIV-infected children (probably a small proportion) either (a) pass through a transient stage of seronegativity between loss of maternal antibody and endogenous production or (b) never have detectable antibody to HIV; or (c) lose antibody late in infection. Alternative methods for documenting HIV infection in children are being developed, but all the tests have limitations and currently appear to add little to HIV-specific IgG antibody tests in most public health settings.

(4) Because of the incompletely defined spectrum of disease in infancy and childhood and the limitations of current laboratory diagnostic tests, there is no clear standard against which to measure existing or proposed paediatric AIDS definitions. The result has been that in some cases the presence or absence of positive results to tests for serological markers of HIV infection has been the standard for validating the case definitions. Such studies should be interpreted with caution, bearing in mind that (a) being HIV-infected is not the same as having AIDS, although infection is an absolute precondition for the latter; (b) what is in fact being measured in such studies is not the sensitivity or specificity but the predictive value of the case definitions for HIV seropositivity. This predictive value will vary according to the HIV seroprevalence in the population studied.

(b) Existing case definitions for paediatric AIDS

The 1987 revision of the Centers for Disease Control (CDC)/WHO case definition[1] is highly specific for HIV-related disease. In settings where diagnostic procedures such as confirmatory serology, biopsy, and culture are routinely performed, this case definition detects most cases in children with serious HIV-related disease. However, because of the complexity of the case definition and its dependence on a specific diagnosis, its applicability is limited. The WHO clinically oriented (Bangui) case definition[2] is somewhat simpler, but misses children with certain HIV-related clinical syndromes such as pulmonary disease. The WHO Bangui definition has a lower specificity, unless accompanied by laboratory evidence of HIV infection.

(c) Case definition evaluations

Preliminary evaluation of the CDC/WHO case definition for paediatric AIDS has been carried out in Belgium, Rwanda, the USA and Zaire. The United States and European

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[1] Weekly Epidemiological Record, 63: 1-7 (1988)

[2] Weekly Epidemiological Record, 61: 69-73 (1986)

studies began with clinical case series of known HIV-infected infants and assessed the proportion of cases meeting the case definition. In the series most children fulfilled the CDC/WHO case definition and nearly all the children who died did. The WHO Bangui case definition included the younger children in the series with wasting disease, but missed some with pulmonary disease. The studies in Africa were cross-sectional, were carried out in hospital medical wards, and measured the predictive value of the WHO Bangui definition against HIV seropositivity. In these studies (in wards where the HIV seroprevalence was 10-30%), only half of the children meeting the WHO Bangui case definition were seropositive. Of the HIV seropositive children fewer than half met the Bangui case definition.

2.2.3 HIV prevalence surveys

Serosurveys in pregnant women have documented levels of HIV infection from zero to under 0.1% in some areas, to over 20% in certain age groups in some urban areas of Central Africa. In areas where most infections in women are related to intravenous drug use, populations at higher than average risk tend to be concentrated in certain districts within cities and in certain socioeconomic groups. In contrast, in areas where heterosexual contact is the primary route of infection in women, risk groups among women cannot be as readily defined. While prostitutes in those areas have the highest rates of infection, a large proportion of infections are in women who have had few sexual partners. Urban rates of infection have been much higher in general than rural rates. Rural areas affected by HIV infection tend to be those lying along communication routes or those with high levels of population migration.

An important development has been the use of blood samples collected on filter paper for HIV antibody testing. In the USA this method has been applied to blood samples routinely collected from the newborn for screening for metabolic disorders (e.g., Phenylketonuria). The samples are unlinked (the identifying information is removed but some demographic data are retained) before testing. Through these studies HIV seroprevalence levels among childbearing women from different states in the USA have been determined; the preliminary results range from under 1 per 10 000 to over 100 per 10 000.

While early serological surveys tended to be convenience samples, such as of persons on a hospital ward or attending a clinic, much attention has been given recently to developing a more rigorous methodology for such surveys, covering for example the representativeness of the sample, the sample size, quality assurance for the laboratory testing process, and the use of linked or unlinked testing. Because participation bias (the differences between persons consenting to being tested as compared with those refusing) can make a survey unreliable, health authorities in many areas are including unlinked anonymous HIV screening as one facet of their HIV surveillance strategy.

Only limited serosurveys in children have been conducted. However, certain studies of the HIV testing of defined groups of children, accompanied by an assessment of the possible risk of HIV exposure, have been helpful in confirming the routes of transmission to children. These are transmission from an infected woman to her fetus or infant, blood, sexual transmission (in older children) and, in rare instances, breast-feeding.

3. RECOMMENDATIONS AND RESEARCH NEEDS

3.1 Transmission, natural history, and diagnosis of HIV infection

3.1.1 Transmission from an infected woman to her fetus or infant

The need to determine the overall rate of transmission from an infected woman to her fetus or infant and the factors that influence this rate are of high priority. The rate is currently estimated to range between 10% and 50%. Ideally the rate can be determined by studies of infants born to HIV seropositive mothers using a test that diagnoses HIV infection reliably in infants with a high degree of sensitivity and specificity. In the absence of such tests, a lower estimate can be obtained by measuring infant

seropositivity in cohorts followed for 12-18 months. An upper estimate can be obtained by including children who die before this age. This latter estimate could further be refined by attempting to attribute the cause of death to HIV infection or to other causes.

The variations in reported rates of HIV transmission from an infected mother to her fetus or infant may be explained by maternal factors resulting in varying infectivity. To identify maternal factors influencing the risk of HIV infection in infants, studies should be conducted seeking correlations between the rates of transmission from an infected woman to her fetus or infant.

(a) The timing and mechanism of transmission from an infected woman to her fetus or infant could be studied by examining fetuses and the newborn for evidence of established HIV infection. HIV could reach the fetus either by crossing the placenta during pregnancy or by exchange of maternal and fetal blood during delivery. The possibility that obstetrical interventions such as amniocentesis, scalp monitoring during delivery, and forceps delivery might influence HIV transmission should be considered.

(b) What data are available are insufficient to assess the role of breast-feeding as a mode of HIV transmission from a seropositive mother to her infant, and further research in this area should be pursued. However, there appears to be little transmission by this route in comparison with transmission during pregnancy or delivery.

(c) The role of mother's clinical and immunological status during pregnancy and lactation in rates of HIV transmission from an infected woman to her fetus or infant requires further study.

3.1.2 Diagnostic tests for HIV in infancy

The development of new laboratory tests to diagnose HIV infection in the first year of life should be encouraged. Passively acquired maternal antibodies to HIV make current routine tests based on IgG antibody of limited value in this age group. To validate any such new tests, they should be evaluated longitudinally against:

(a) ELISA and Western blot seropositivity in the second year of life (after the first birthday, the majority of uninfected children will have lost passively acquired maternal antibody); and

(b) the appearance of HIV-related disease.

There is a need to adapt one or more of the improved diagnostic tests for HIV infection in infants for use in laboratories with limited equipment. Such tests are likely to be based on the detection of HIV antigen or antibody, by for example an agglutination indicator reaction.

Long-term follow-up of infants who have lost maternal antibody will be necessary to confirm the absence of infection. There have been a few reports of children and adults who are infected but remain seronegative, or later become seropositive.

3.1.3 Pregnancy and HIV infection

To define the effects of maternal HIV infection on the outcome of pregnancy, the frequency of (a) stillbirths, (b) miscarriages, (c) low birth weight, and (d) premature delivery should be compared in HIV seropositive and seronegative pregnant women.

The potential effect of HIV infection on pregnant women has two related aspects: (1) the impact of pregnancy on the rate of progression of maternal HIV infection during or after pregnancy, and (2) the degree to which the mother's illness affects her ability to care for her children and the likelihood of her carrying other pregnancies to term. These may be best evaluated by studying large cohorts of HIV seropositive women.

3.1.4 Natural history of HIV infection in children

There is a need to elucidate fully the natural history of HIV infection in children, with recognition of the fact that it may vary with host, environmental, or viral factors. Specific prognostic indicators need to be identified. Comparative studies will help to identify the contribution that environmental factors make to the natural history. These studies would be greatly enhanced by the availability of accurate diagnostic tests for HIV infection in infancy. Identification of co-factors influencing the morbidity and mortality of HIV infection in infancy and childhood is also important. Large cohort studies are required in areas with different socioeconomic and environmental backgrounds. Comparisons should be made between the outcome for seronegative and seropositive children of seropositive mothers and the outcome for children of seronegative mothers.

3.2 Surveillance, forecasting, and impact assessment

3.2.1 AIDS case surveillance

(a) Modifications of the WHO Bangui clinically oriented case definition

Ideally, one universal definition should be adopted for paediatric AIDS. However, it must await further review as experience with current case definitions is limited and few systematic evaluations of those definitions have been carried out. The current CDC/WHO and WHO Bangui definitions should continue to be used, but the following modifications for the WHO Bangui definition should be considered:

(1) Testing for serological markers of HIV infection should be carried out whenever HIV infection is suspected. This is crucial, not only for adequate case surveillance but also for clinical management. Reported cases should be classified according to the presence or absence of results from tests for serological markers of HIV infection. In high prevalence areas where resources are limited, ELISA or other tests may be used alone, in the presence of illness suggestive of HIV-related disease. However, wherever possible the use of supplementary tests such as Western blot is recommended. Infection in the mother can be used as a surrogate laboratory marker for young children with suspected AIDS.

The use of antibody tests alone will result in some uninfected infants born to HIV seropositive mothers being wrongly classified, but at present no alternative tests can be recommended for routine use.

Since AIDS has been documented in HIV seronegative children, those children should not be excluded if they have compatible symptoms, but they should be classified separately.

(2) Persistent or severe lower respiratory tract infection should be added as a major sign in the WHO Bangui case definition. This might replace the minor sign persistent cough.

Other points for consideration in relation to the WHO Bangui case definition are given below, but information is insufficient to warrant modification of the definition at present.

(1) In the WHO Bangui case definition for children, the major signs are associated with more severe illness, the minor signs are more specific for HIV infection. While the present division into major and minor signs is reasonable, further evaluation is needed to determine if it would not be better to have a single list of signs and symptoms given equal weight or an assignment of points to each sign or symptom so as to provide a minimum AIDS score.

(2) Although chronic diarrhoea is a frequent and debilitating manifestation of HIV-related disease, for surveillance purposes it appears to add little to the definition beyond the other major signs of persistent fever and weight loss, with which it is highly correlated in AIDS patients.

(3) Several of the signs in the WHO Bangui definition are poorly defined. Particularly so are the "persistent" symptoms, which require a regular follow-up of patients or a careful history and an accurate informant. The definition correctly reflects the chronic nature of HIV immunodeficiency; however, the requirement of persistent symptoms results in the exclusion of young children who may die from a single fulminant infection before their immunodeficiency is recognized.

(4) A substantial proportion of HIV-infected children die in the first year of life, not surviving long enough to receive an adequate evaluation. Therefore the possibility of adding "death" or "death due to medical illness" as a major clinical sign for children who are documented to have been born to an HIV-infected mother was discussed, but it was felt that existing data were insufficient to recommend adoption.

(5) HIV-infected children are often first detected by their lack of response to appropriate therapy for the presenting complaint (e.g., pneumonia, oral thrush). The phrase "unresponsive to appropriate therapy" might be added to the signs. However, this change might cause practical difficulties and could end up creating as many problems as the term "persistent", particularly in relation to children without a regular medical follow-up.

(6) Certain features of HIV-related disease in childhood, such as encephalopathy, are not included in the WHO Bangui definition. The advantages of adding new signs and symptoms to the case definition need to be weighed, when more data are available, against the goal of simplicity.

(7) The possibility was suggested of stratifying the WHO Bangui definition by age, with diagnostic algorithms for children under 1 year of age different from those for over 1 year of age. This would solve some of the problems of diagnosis. As an alternative, instead of altering the definition itself, reported cases could simply be categorized according to age at diagnosis.

(b) Case definition research needs

More data are needed in several areas before any major revision of the case definition can be recommended. The following research approaches are recommended.

(1) Review of current surveillance practices

A survey in several countries exploring paediatric AIDS surveillance issues should be undertaken in the near future. The goal of such a survey would be to ascertain what definitions are in use and how they are being implemented, and to pinpoint difficulties in the definitions as well as in the mechanics of case reporting. Such a survey would involve extensive country visits, discussions with a variety of public health officials and clinicians, and visits to medical facilities.

(2) Formal evaluations of case definitions

A list of clearly defined core signs and symptoms should be established to be included in any evaluation of paediatric AIDS case definitions. Basic protocols for case definition studies could also be established to assist clinicians in various countries to evaluate existing and proposed case definitions using existing cohorts or case series. Such protocols would

ensure that certain important clinical and laboratory variables are consistently recorded in any future study evaluating case definitions. It would also be useful if appropriate computer software to assist in the collection and analysis of data from case definition studies were developed. An important consideration in case definition studies is the population chosen for study (such as children hospitalized for illness or being followed up in a prospective cohort). While case series of children diagnosed as having HIV-related disease are a convenient sample for study, such studies should continue to be interpreted with caution.

Findings from special case definition evaluations and from prospective cohorts, cross-sectional studies, or clinical case series that shed light on case definition issues should be communicated to WHO. It is anticipated that enough data will become available over the next 6-12 months to warrant a further meeting of a technical working group and eventually an improved paediatric AIDS case definition.

(3) Association of HIV infection and other diseases

Many infections that are common in children, particularly in developing countries (such as pneumonia and diarrhoea), mimic the HIV infection in their clinical signs. In addition, certain diseases such as tuberculosis and measles are considered to be more severe in HIV-infected children, and their occurrence may hasten the progression of HIV-induced immunodeficiency. Clinical studies exploring the interaction between these diseases and HIV infection are of high priority. They will shed light on a variety of questions, including the clinical spectrum of HIV infection, the pathogenesis of the infection, and appropriate treatment strategies. The findings of these studies may also indicate how the current case definitions could be improved.

(4) Evaluation of tests for HIV diagnosis

Although new laboratory tests for HIV diagnosis in infants are being developed and evaluated, the only readily available and practical tests at present are HIV IgG antibody tests. Thus determination of the time of loss of maternal HIV antibody in children from different regions in relation to different types of HIV antibody tests is important. This will help to clarify for the different ages how much error results from the use of antibody seropositivity as the sole serological marker of infection.

3.2.2 HIV prevalence and incidence studies

WHO guidelines are in preparation for carrying out serosurveys in the most efficient and appropriate way for public health purposes. In addition to such serosurveys, careful incidence studies of cohorts will document risk factors for infection and help in the assessment of infectivity in different settings. Since incidence studies are difficult, the bulk of data on the extent of infection in different regions and population groups will continue to come from prevalence surveys. If conducted consistently, with appropriate sampling strategies and an accurate description of the populations tested, prevalence surveys may permit reasonably accurate forecasting and evaluation of the effectiveness of preventive efforts.

3.2.3 Modelling

Despite the uncertainties in many of the parameters relating to HIV infection in children, modelling the impact of the HIV/AIDS epidemic in children may prove easier and more reliable than in other population groups. The development of good models and the reassessment of existing models as new data become available are of high priority.

Data are needed to assess the current and future impact of HIV-related disease in children (which is mostly due to transmission from an infected woman to her fetus or infant), including information of good quality in each of the areas discussed above in relation to paediatric HIV/AIDS research needs. The data should be collected in different sites over different periods of time, attention being paid to the methodology. In establishing a data base for an accurate assessment of trends and for reliable predictions, several studies are of particular importance:

(a) seroprevalence studies in pregnant women and in women of childbearing age;

(b) estimates of the overall rate of transmission from an infected woman to her fetus or infant and of factors affecting transmission (e.g., the stage of maternal HIV infection);

(c) studies of biological and psychosocial factors affecting reproductive decisions and the fertility rate in HIV-infected women; and

(d) rough estimates of the rate of progression to disease in HIV-infected infants.

3.2.4 Analysis of mortality and morbidity trends

Studies of overall and cause-specific infant and childhood mortality trends in different regions where good HIV seroprevalence data are available are strongly recommended. Where existing records on deaths are insufficient, special in-depth studies of mortality may be required.

Trends in deaths due to specific illnesses can also be helpful. They can be examined in special studies, such as of mortality rates in diarrhoea treatment centres and the relationship between mortality and HIV infection.

In longitudinal cohort studies, morbidity and mortality should ideally be compared in three groups:

- HIV-infected children born to HIV-infected women
- Uninfected children born to HIV-infected women
- Uninfected children born to uninfected women.

Morbidity and mortality are of particular interest in uninfected children born to HIV-infected women. The extent to which HIV disease in the mother (or in both parents) may influence the health and social well-being of HIV-uninfected children in the family is not at present clear.

3.2.5 Community impact studies

Studies assessing the impact of childhood HIV-related disease on health systems and on the socioeconomic status of the family and community are recommended. The high potential cost of the disease will be evident, particularly in areas where a high prevalence of infection exists, and recording the various details of the cost will stimulate preventive efforts.

4. SUGGESTIONS FOR EARLY ACTION

The highest priority for surveillance should be given to:

- studies to assess the overall impact of HIV infection on child health;
- a survey of surveillance practices in different areas;
- the establishment of a basic protocol for case definition studies; and

- periodic meetings, organized perhaps at the same time as other conferences, to reassess the data so that changes in case definitions can be recommended as necessary.

To examine the interrelated issues of HIV transmission, the natural history of the disease, and the diagnosis, large carefully designed cohort studies of children born to HIV-infected women will, although difficult and labour-intensive, continue to provide the most information. Several such studies have already begun. The studies should include control groups of women not infected with HIV and their infants, and priority should be given to maintaining the follow-up at a high level. Although a single protocol is not essential, some degree of coordination will facilitate comparison of the results between studies. WHO might develop a data base with simple summary data from each of these studies, to be updated periodically. Sharing of laboratory specimens would also increase the usefulness of research laboratories with expertise in particular tests.

The questions raised by HIV infection and pregnancy will prove difficult and probably require the long-term follow-up of large numbers of women. As the majority of such studies are at present in the process of preparation, WHO could assist with methodological issues and play a coordinating role.

ANNEX

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Annex 1

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