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REPORT OF THE FIRST MEETING OF THE COMMITTEE ON ORTHOPOXVIRUS INFECTIONS, GENEVA, 3 - 5 MARCH 1982

In accordance with resolution WHA33.4, 'Global Smallpox Eradication', which endorsed the 19 recommendations of the Global Commission for the Certification of Smallpox Eradication[1], a Committee on Orthopoxvirus Infections was established by the Director-General of the Organization in 1981 to advise on the post-smallpox eradication policy in order to maintain the achievement of smallpox eradication permanently. The first meeting of this Committee was held from 3 to 5 March 1982 in Geneva.

The meeting was opened by Dr I. D. Ladnyi, Assistant Director-General and Dr A. Zahra, Director, Division of Communicable Diseases, on behalf of the Director-General. Dr F. Fenner was elected Chairman, Dr S. S. Marennikova, Vice-Chairman, and Drs K. Dumbell and D. A. Henderson, Rapporteurs. A list of participants and the agenda are attached as Annexes 1 and 2.

The meeting reviewed the progress made on the implementation of the World Health Organization's (WHO's) post-eradication policy as recommended by the above-mentioned resolution and advised on future activities under seven groups of topics.

1. Vaccination Policy (Global Commission recommendations 1 and 2)

WHO has been informed that routine vaccination has been officially discontinued in 149 of the 158 Member States and Associate Members. Information available to the Committee (3 March 1982) showed that in two countries (Egypt and Kuwait), routine vaccination was still being practised; in six the present status was not known. Further steps are continuing to be taken to encourage all countries to cease routine vaccination.

During the past year, WHO inquired of all known vaccine producing laboratories about current production and distribution of smallpox vaccine. Of 80 producers questioned, 77 replied and of these, 54 indicated that they had stopped production. Of the 23 laboratories now producing vaccine, most were producing less than two million doses per year and only five indicated that they planned to continue production for more than five years.

The Committee expressed satisfaction with progress being made in the discontinuation of smallpox vaccination and strongly reaffirmed the recommendation of the Global Commission that: "no one except investigators at special risk should be vaccinated in any country including those where monkeypox cases have occurred". In addition to the few investigators engaged in orthopoxvirus research, the Committee agreed that those engaged in vaccine virus production should also be included among the small group for whom continuing vaccination is recommended. The Committee believed that it would be important and desirable again to draw to the attention of the World Health Assembly that complications following vaccination can be extremely serious and sometimes fatal and that there is no justification now to vaccinate any but the few workers noted above. Moreover, it was noted that unnecessary vaccination may be regarded as constituting medical malpractice. The Committee recommended that WHO contact all laboratories continuing to produce smallpox vaccine to advise them of these observations and to request that they cease further commercial distribution of vaccine.

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[1] The Global Eradication of Smallpox. Final Report of the Global Commission for the Certification of Smallpox Eradication, Geneva, December 1979. History of International Public Health, No. 4. World Health Organization, Geneva, 1980. Refer to pages 12-15.

Two countries (United Kingdom and Finland) have informed WHO that smallpox vaccination of military personnel has been discontinued. National health authorities should be advised that continuing vaccination of such personnel involves risk both to the vaccinees and to susceptible contacts. Since increasing numbers of vaccinees and their contacts will not have been previously vaccinated, the risk of serious complications will inevitably increase. Accordingly, the Committee believes that vaccination of military personnel should be discouraged.

All countries have now notified WHO that international certificates of smallpox vaccination are no longer required of travellers. During the past year, the International Health Regulations have been amended to delete all reference to smallpox vaccination. Nevertheless, some embassies and consulates, as well as travel agencies, unaware of the World Health Assembly's resolution 33.4, 'Global Smallpox Eradication', that such certificates are no longer required, advise travellers erroneously. The Committee encouraged WHO to publicize more widely that smallpox vaccination certificates are no longer required. It was suggested that appropriate announcements should appear periodically and prominently in the Weekly Epidemiological Record and the booklet entitled "Vaccination Certificates for International Travel and Health Advice to Travellers". The Committee was informed that action has already been taken to delete the section for smallpox vaccination from WHO's standard international vaccination certificates.

2. Reserve Stocks of Vaccine (Global Commission Recommendations 3, 4, 5 and 6)

Pursuant to recommendations of the Assembly, WHO has established two refrigerated depots for vaccine storage (Geneva and New Delhi) with an existing reserve sufficient to vaccinate more than 200 million persons. The Committee visited the Geneva depot and found the conditions of storage eminently satisfactory. At the vaccine storage depot in New Delhi, where some six million doses of vaccine are kept, problems have been experienced with temperature fluctuation which has ranged from $-20^{\circ}C$ to $-10^{\circ}C$. The Committee expressed the view that, based on present knowledge, this should not have affected vaccine quality. However, the Committee recommended that minor repairs suggested by a consultant should be carried out and that WHO should plan to monitor the titre of each batch of smallpox vaccine in the New Delhi storage facility annually for the foreseeable future. The Committee also suggested that other WHO programmes should be invited to consider use of part of this freezer space thus encouraging continuing oversight of its function. For vaccine stored in Geneva, WHO has developed a 10 year plan which provides for satisfactory monitoring of the potency of the stored vaccine according to the procedure set up in the document "Management of reserve stocks of vaccine in the post-smallpox eradication era" (WHO/SE/80.158 Rev.1). The Committee endorsed this plan. Note was made of the fact that the current WHO smallpox vaccine requirement[1] calls for a three year expiry date of freeze-dried smalllpox vaccine following release from the manufacturer or after repeat titration. The Committee recommended that this provision be waived, assuming that sample testing showed stability of vaccine potency for the batches in storage.

Additional substantial quantities of vaccine are known to be held in other countries. The Committee believes that the monitoring and titration of such stocks is a national responsibility and that WHO should offer assistance only when special problems arise.

The Committee urged that WHO implement, as soon as possible, the Assembly's recommendation that seed lots of vaccinia virus suitable for the preparation of smallpox vaccine be maintained in WHO collaborating centres in Atlanta, Paris and Tokyo.

The Committee endorsed the policy that WHO emergency vaccine reserves be released only on clinical and laboratory confirmation of a diagnosis of smallpox. The Committee recognized that difficult problems might be encountered by WHO in the allocation of vaccine resources by area and by country should a case be identified. Expert epidemiological appraisal and assessment of risk would be required. The Committee is prepared to provide guidance to the Organization at short notice as may be appropriate.

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[1] Requirements for biological substances. Wld Hlth Org. techn. Rep. Ser., 1966, 323.

(Refer to page 71.)

3. Investigation of Suspected Cases (Global Commission Recommendations 7 and 8)

The Committee expressed satisfaction that the Organization has continued to participate actively in documenting rumours of the occurrence of smallpox cases whenever they have occurred. Since January 1979, 124 such rumours from 55 countries have been investigated, most of which have been misdiagnosed cases of chickenpox, measles and other skin diseases. None have been smallpox. The number of rumours reported has decreased with time, 63 rumours having been reported in 1979, 31 rumours in 1980 and 30 rumours in 1981.

The Committee endorsed the document "Management of suspected cases of smallpox in the post-eradication era" (WHO/SE/80.157 Rev.1).

The Committee noted particularly the clear need for WHO "to maintain an effective system to coordinate and participate in the investigation of suspect smallpox cases throughout the world". Several rumours, for example, have provoked widespread international alarm which required immediate and critical evaluation to sustain public confidence in the eradication of smallpox. The Committee was concerned, however, that confirmation with regard to some of the rumours has extended over some months because of delays in response by national health authorities. The Committee urged that all rumours be promptly investigated by competent health personnel and the results reported to WHO within 30 days. WHO assistance at national, regional or international level, as appropriate, should be freely sought if there were questions or potential delays.

4. Laboratories Retaining Variola Virus (Global Commission Recommendations 9 and 10)

The Assembly recommended that no more than four WHO collaborating laboratories "be approved as suitable to hold and handle stocks of variola virus" and that these be inspected periodically. At present, variola virus is being stored in four laboratories, of which three are collaborating centres. Only one (United Kingdom) has been conducting laboratory studies with the virus during 1981. Renovation at the Centers for Disease Control (USA) will permit studies to recommence there in about a month's time; renovations at the Research Institute of Virus Preparations (USSR) are 70% complete and work is expected to recommence there in eight to 10 weeks' time. Each of the laboratories retaining variola virus has been inspected twice by WHO staff and consultant teams between February 1979 and March 1982 and further periodical visits are planned. The one laboratory which is now using the virus in experimental studies meets accepted standards for containment. The others were found to be storing the virus safely. The laboratories in the USA and the USSR will be revisited by international inspection teams before they recommence work with variola virus.

The Committee recommended that WHO continue to inspect these laboratories regularly to ensure that WHO requirements are being met, and that each international inspection team, following evaluation, should file a detailed report of its findings with WHO, the responsible national health authority and the laboratory. Such records should be available for review by any Member State.

The Committee wished to express its special gratitude for the cooperation of the governments of the United Kingdom, the USA and the USSR in undertaking the renovation of their laboratories to permit the necessary, valuable research work to be completed and asked WHO to convey its special thanks.

The Committee recommended that because important research studies are still in progress, the decision regarding retention of variola virus be reconsidered by the Committee on Orthopoxvirus Infections in 1985 and, depending on the outcome of these deliberations, further consideration be given at that time to the appropriate disposition of the virus.

5. Human Monkeypox (Global Commission Recommendation 11)

The Committee reviewed and endorsed the strategy of the current programmes for surveillance of human monkeypox in west and central Africa which has been developed according to the recommendation that "in collaboration with country health services, WHO should organize and assist a special surveillance programme on human monkeypox". Such programmes consisted of epidemiological and laboratory investigation of reported human monkeypox cases in all these areas; special serological investigation for orthopoxvirus antibody, including monkeypox antibody, in unvaccinated children; and development of health institution-based surveillance in selected areas of west and central Africa.

5.1 Epidemiology of monkeypox

The total number of known cases of human monkeypox since 1970 now stands at 58, with three further clinical cases already shown to be positive by electron microscopy and awaiting the results of virus culture. Recent observations have not changed the previous picture of the age-incidence, severity, and low transmissibility of this disease. Attention was drawn to the frequency with which a localized lymphadenopathy is encountered as a clinical feature. This was not a feature of smallpox in these areas and it may indicate a route of entry involving local trauma or biting insects. Some of the monkeypox cases had presented complaining of fever and swollen glands, and the rash developed a day or two later. It was suggested that surveillance activities should be on the look-out for further similar cases to try to determine the frequency of lymphadenopathy in human monkeypox and that it might be instructive to examine some serum specimens from cases of fever and lymphadenopathy who did not develop a skin rash, if such cases could be readily identified.

The Committee felt that the most important features of continuing surveillance were to note any change in the present low level of occurrence and transmissibility and to learn more of the natural history and epidemiology of the disease. For this purpose it would be most effective to concentrate efforts on limited areas of high incidence which are situated in Equateur, Kasai Oriental and Bandundu regions of Zaire. The majority of cases have been detected in these regions during the last 10 years and mobile teams are continuing to play an essential role in surveillance, for investigation of outbreaks and to maintain cohesion and interest among the static health units involved. The Committee did not consider that it would be cost-effective to develop the detection system now operating in Zaire in other countries of west and central Africa. Present data indicated that monkeypox was not of public health importance even in areas of highest incidence.

5.2 Serological survey 1981/82

From 26 to 29 October 1981, an informal meeting of scientists was held at the Centers for Disease Control, Atlanta, and at Duke University Medical Center, Durham, USA, in order to discuss techniques for the assay of various human and animal sera for antibodies to monkeypox virus and other orthopoxviruses.

During 1981, about 10 000 serum speciemns were collected, mostly from apparently unvaccinated persons, in order to study the prevalence of human monkeypox antibody in persons who inhabit the areas where the presence of a monkeypox reservoir has been suspected. The Committee considered the interim results of the laboratory investigation of sera. The survey was conducted in Congo, Ivory Coast, Sierra Leone and Zaire and improvements and standardization of the technique for serological screening tests have given results which are positive in a high proportion of persons with evidence of previous vaccination. There was good correlation between the results of various tests. After discussion the Committee recommended that future initial screening for orthopoxvirus antibody should be done by the HI test using the protocol developed at the Centers for Disease Control, Atlanta, USA.

During the survey in the field, some difficulties had been encountered in determining those persons who had not been vaccinated. Absence of a scar was not completely reliable as the jet injector had been widely used in these countries; nor could reliable histories always be obtained. As the unvaccinated group was the most important for the investigation of monkeypox prevalence, it had been decided to exclude from further serological examination all those in whom there was evidence or even suspicion of previous vaccination. Since the last cases of smallpox in these countries were detected in 1969-1970, the Committee recommended that sera from age groups over 10 years should be excluded from laboratory investigation as positive results that might be obtained with such sera could not be reliably interpreted.

The interim results of laboratory investigations (performed at the Centers for Disease Control, Atlanta, and the Research Institute of Virus Preparations, Moscow) have shown the occurrence of a number of positive results for orthopoxvirus antibody in unvaccinated children under 10 years of age. At least some of them were likely to have been due to infection with monkeypox virus but there might be other, as yet unrecognized orthopoxviruses producing human infection in these areas and further investigation is required.

Mindful of these considerations, the Committee recommended that the current laboratory investigation of serum specimens should be completed as soon as possible so that those whose sera showed the presence of specific monkeypox antibody should be investigated by field visits.

Meanwhile the Committee noted that certain evidence of infection by monkeypox virus can at present be obtained only by testing suitably absorbed sera by radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA) tests; not all orthopoxvirus-positive sera have an antibody titre sufficiently high to permit this. Other kinds of specific tests now in course of development, such as radioimmunoprecipitation (RIP) and tests utilizing suitable species-specific monoclonal antibodies, offered the possibility of overcoming the difficulty and the Committee expressed its anxiety that these tests should become operative for testing field specimens as soon as possible.

The Committee expressed the hope that vaccination will be totally discontinued in the countries of west and central Africa, even where monkeypox has been found to occur, as recommended by the Global Commission (recommendation 1).

5.3 Plan for monkeypox surveillance in west and central Africa, 1982/83

The Committee endorsed a plan to maintain the special programme on monkeypox surveillance in four countries of west and central Africa (Congo, Ivory Coast, Sierra Leone and Zaire). The plan includes the epidemiological investigation in all four countries of persons (under 10 years of age and unvaccinated) whose serum specimens showed presence of monkeypox antibody, and continuation of special surveillance supported by mobile surveillance teams and health institutions in Zaire. Needless to say, if a human monkeypox case is reported, this will take priority for investigation. The Committee considered that collection of specimens from varicella patients should only be carried out in Zaire.

6. Laboratory Investigation (Global Commission Recommendations 12, 13, 14 and 15)

The Committee recognized the special nature and value of the research being conducted and strongly supported its continuance at least until 1985, to complete research which is essential for maintaining post-smallpox eradication surveillance. Important studies for the post-smallpox surveillance programme include: the development of simple and reliable screening tests for orthopoxvirus antibody and, more importantly, the development of reliable tests for antibody specific to monkeypox virus and other species of orthopoxvirus. Further development of these methods involves the production of monoclonal antibodies specific for the different species of orthopoxvirus. Also important are increasingly detailed studies of DNA from monkeypox and variola virus and studies of the persistence of monkeypox virus in various animals.

The Committee reviewed the current research work in progress at collaborating centres.

6.1 Radioimmunoprecipiation (RIP) tests and monoclonal antibodies for detection of monkeypox specific antibodies in human and animal sera (Dr W. K. Joklik, Duke University Medical Center, Durham, USA and Dr J. H. Nakano, Centers for Disease Control, Atlanta, USA)

Work on development of radioimmunoprecipitation tests as a simple and reliable test for species-specific antibodies and efforts to select suitable species-specific monoclonal antibodies have been proceeding but these tests are not yet applicable to monkeypox surveillance or for investigation of sera collected from suspected cases of smallpox. It is important that the RIP test be available as soon as possible to confirm or assist with the appropriate interpretation of orthopoxvirus positive sera collected from unvaccinated children in west and central Africa. The Committee recommended that a high priority should be given to the development of the RIP test and the preparation of monoclonal antibodies, which would eventually be the method of choice for these investigations.

6.2 Analysis of DNAs of various orthopoxviruses (Dr K. R. Dumbell, Centre for Applied Microbiology and Research, Porton Down, UK, Dr J. H. Nakano, Centers for Disease Control, Atlanta, USA and Dr S. S. Marennikova, Research Institute of Virus Preparations, Moscow, USSR)

DNA analysis of variola, monkeypox, and other orthopoxviruses is proceeding with the objectives of 1) producing a 'library' of DNA maps for the classification and identification of orthopoxviruses and 2) providing a detailed comparison of the degree of relatedness between variola virus and other orthopoxviruses, in particular monkeypox.

Cloning of variola DNA into E. coli to enable efficient studies to be safely made of this genome, is also being conducted. Some clones of a portion of the Harvey genome have been constructed and others will be available in 1983.

6.2.1 Safety aspects of work with variola DNA

The Committee considered the safety aspects of studies on variola and other orthopoxvirus DNA. There are good theoretical reasons supported by abundant practical experience that orthopoxvirus DNA is non-infectious and the preparation of the DNA involves sequential procedures, each of which is a potent inactivator of infectious virions. However, it has been shown that orthopoxvirus DNA can be replicated and expressed as infectious virus in cells which are co-infected with a different orthopoxvirus. The Committee agreed that there is no hazard attached to the handling of variola DNA by designated personnel in laboratories in which there was total exclusion of viable poxviruses; nevertheless, the Committee recommended that collaborating centres should not transmit intact variola DNA to other laboratories. This recommendation does not apply to fragments of variola DNA or to such fragments cloned into suitable vectors. The Committee agreed that such clones should be available to interested laboratories under the conditions imposed by the guidelines for recombinant DNA, which are applicable in the country or countries concerned.

6.3 Pathogenesis of monkeypox and viral persistence in animals (Dr T. Kitamura, Division of Poxviruses, National Institute of Health, Tokyo, Japan, and Dr S. S. Marennikova, Research Institute of Virus Preparations, Moscow, USSR)

It was reported that monkeypox virus produced generalized disease and death after experimental inoculation in cynomolgus monkeys but that one species of African monkey tested suffered only a trivial or subclinical illness with minimal reaction at the site of inoculation. Studies are in progress to assess the persistence of monkeypox virus in tissues of a species of insectivorous shrew (Suncus muris).

The Committee recommended that the studies in progress should continue as speedily as possible as the results will be important when the recommendations of the Global Commission are considered in 1985 and plans are developed to cover the succeeding period.

7. Archives and Publications (Global Commission Recommendations 16 and 17)

7.1 Archives

The records of the smallpox eradication programme have now been established in an archival mode. In addition to the archives themselves, there is a comprehensive inventory and guide indicating what is in each of the files. The archives will be retained at WHO. So far as access is concerned, it is the opinion of WHO's legal office that the files, being essentially of a scientific nature, will eventually be able to be made accessible to historians on grant of a waiver by the Director-General. The Committee endorsed this archiving programme and complimented WHO on its initiative.

7.2 Publications

Plans have been developed to publish a book of about 500 000 words dealing comprehensively with relevant scientific, operational and administrative aspects of the smallpox eradication programme. A five-person editorial group comprising Drs Arita, Fenner, Henderson and Ladnyi and Mr Loveday would bear primary responsibility for preparation and editing of material for the book. They will draw extensively on existing information and that provided by others and, during the course of preparation, will circulate widely draft copies of chapters to knowledgeable persons. Approximately three years will be required to complete the work.

The Committee endorsed the plan.

Other publications that have been supported by WHO include books dealing in detail with the eradication programmes in Bangladesh, Ethiopia, India and Somalia.