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Report of the meeting of the Ad Hoc Committee on Orthopoxvirus Infections. Geneva, Switzerland, 14-15 January 1999

World Health Organization
Department of Communicable Disease Surveillance and Response

Contents

Introduction	1
Recent monkeypox outbreaks in the Democratic Republic of Congo	1
Review of the report of the 1994 Ad Hoc Committee on Orthopoxvirus Infections	2
Work in WHO Collaborating Centres	3
Analysis and sequencing of variola virus genomes	3
Biosecurity and physical security of WHO collaborating laboratories	4
Smallpox vaccine stocks and production	4
Deliberate release of smallpox virus	4
Survey of WHO Member States latest position on destruction of variola virus	4
Recommendations	5
List of Participants	6

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Introduction

Dr Lindsay Martinez, Director, Communicable Disease Surveillance and Response (CSR), welcomed participants and opened the meeting on behalf of the Director-General of WHO, Dr G.H. Brundtland as well as Dr David Heymann, Executive Director, Communicable Diseases. Dr Martinez indicated that the objectives of this third meeting of the Ad Hoc Committee was to a) assess the public health threat of human monkeypox, based on the report of the WHO Technical Advisory Group on Human Monkeypox; b) review the status of recommendations made by the 1994 Ad Hoc Committee on Orthopoxvirus Infections including reviewing all relevant information pertaining to possible destruction of the stocks of variola virus in 1999, and advising WHO accordingly and c) evaluate the 1994 recommendations based on current scientific knowledge and capabilities in order to formulate recommendations for research and other public health action needed on monkeypox and variola virus.

Dr D.A. Henderson was appointed Chairperson and Dr J.D. Williamson was appointed Rapporteur.

Dr Henderson noted with regret that Dr Frank Fenner, the Committee's Chairman since its inception, was unable to attend the meeting because of illness. Another great loss to the work of the Committee and of the Organization was Mrs Karin Esteves who died within the past year. Mrs Esteves dedication and abilities will be difficult to replace.

Recent monkeypox outbreaks in the Democratic Republic of Congo (DRC)

The Ad Hoc Committee considered the report of the Technical Advisory Group on Human Monkeypox and the current monkeypox situation in central Africa in light of several reports of disease outbreaks which were alleged to have different epidemiologic features than previously reported. In particular, purportedly increased proportions of secondary cases and rates of interhuman transmission were of great concern. Past meetings of the Ad Hoc Committee on Orthopoxvirus Infections had reviewed the status of this rare disease and advised continued monitoring. The Technical Advisory Group was convened to review the currently available evidence and formulate recommendations for appropriate action.

From 1970 to 1992, 418 human monkeypox cases were reported and confirmed from Western and Central Africa, mainly from DRC and, of these, 338 cases were found by WHO intensive surveillance in the period 1981 to 1986. Since February 1996, there have been over 800 suspected cases of human monkeypox reported from DRC, raising questions in DRC and internationally as to whether monkeypox incidence and transmission have increased to a level posing a public health threat. Smallpox vaccination, which protects against monkeypox, stopped in DRC in 1981; hence much of the population is susceptible to monkeypox infection. Three different DRC/WHO/international teams have investigated the reported outbreak. While very valuable epidemiologic information and laboratory specimens were collected, a full

understanding of the situation has been restricted by civil and military disorder together with lack of continuity in team composition and infrastructural support.

Most suspected human monkeypox cases were studied retrospectively. The secondary attack rates within households appeared to be about 9%, similar to the rate from 1981 to 1986. Over 25 active cases were confirmed as monkeypox by detection of virus. However, serologic studies indicated varicella-zoster and monkeypox viruses were cocirculating, adding to the complexity of surveillance.

Earlier, ecologic studies indicated that a number of animal species caught in monkeypox endemic areas had orthopoxvirus antibodies and monkeypox virus was found in one squirrel in 1985. It is now possible that an epizootic of monkeypox is occurring and humans are being infected due to close contact with infected animals being used as a food source. None of the three investigative missions was able to conduct appropriate ecologic studies.

On the basis of the present data, the human, virologic and ecological aspects of the outbreak could not be clarified. Therefore, it is important that clinical, epidemiologic, laboratory and ecologic features of the current cases of rash illness in the areas be investigated carefully and promptly. A prospective surveillance and research programme, including improvement of diagnostics' specificity and sensitivity, will be the optimal way to clarify the situation. This can be facilitated by a reaffirmation of commitment by WHO and collaborating partners following the detailed recommendations of the WHO Technical Advisory Group Meeting on Human Monkeypox convened 11-12 January 1999.

Review of the report of the 1994 Ad Hoc Committee on Orthopoxvirus Infections

The current Ad Hoc Committee heard specific proposals which might require retention of variola virus stocks. These included further development of smallpox vaccines, development of drugs with activity against orthopoxvirus infections, development of laboratory diagnostic tests and public health concern about other human orthopoxvirus infections. Others argued that experiments which require viable variola virus are no longer justified. Such debate covered arguments made previously for either destruction or further retention of variola virus stocks but there were no specific novel proposals. There was agreement with the report of the 1994 Ad Hoc Committee that, although there are minimal hazards associated with the physical containment of laboratories keeping stocks of variola virus, the political drawbacks are considerable.

The Ad Hoc Committee members were not unanimous in their views regarding destruction. Five favoured the destruction of all existing stocks of smallpox virus by June 1999 in accordance with resolution WHA49.10. Two members were in favour of eventual destruction with a review in five years' time and two favoured retention of the stocks. The members who advocated retention of the virus took the view that any potential which might arise in the future for developing scientific information should not be precluded. Although other members agreed that such findings might be useful, they expressed greater concern about the risk of the virus being released.

It was agreed by this Ad Hoc Committee that stocks of archival, cloned DNA should continue to be kept in both WHO repositories and they should include the retention of duplicated stocks of two strains of variola major and one strain of variola

minor. In addition, it was agreed that γ-irradiated, killed variola virus should be kept for use as an essential antigen in laboratory diagnostic tests for human monkeypox virus infection.

Advances in PCR technology have now made it possible to recover fragments of variola virus DNA from inactivated material such as γ-irradiated, killed virus or formalin-treated, infected tissue. It is recognized that such sources of variola virus DNA exist in many laboratories around the world. However, earlier recommendations have been made that PCR amplification of variola virus DNA followed by its subsequent expression by other orthopoxvirus vectors should be prohibited as recommended by the report of the Ad Hoc Committee on Orthopoxvirus Infections, Geneva, 9 September 1994. Such prohibition should also apply to the chemical synthesis of variola virus DNA.

Work in WHO Collaborating Centres

Variola virus stocks were transferred from the WHO Collaborating Centre for Smallpox and other Orthopoxvirus Infections located within the Institute of Viral Preparations, Moscow, to the State Research Center of Virology and Biotechnology (VECTOR), Koltsovo, in September 1994. Permission to work on variola virus was given by the Russian Federation State Committee on Sanitary and Epidemiological Surveillance in May 1995 and a WHO inspection took place in June 1995. VECTOR was designated a WHO Collaborating Centre for Orthopoxvirus Diagnosis and Repository for Variola Virus Strains and DNA in June 1997. The facility at VECTOR has been used for propagation of variola strains to obtain DNA but, apart from one request that has not been followed up, no external request has been received for use of that facility. The WHO Collaborating Centre for Smallpox and other Orthopoxvirus infections located within the Centers for Disease Control and Prevention (CDC), Atlanta, has been used in total for a few weeks only to grow the Garcia-1966 strain of variola virus for collaborative sequencing studies, to provide DNA for studies at Porton, UK, and to check diagnostic variola virus isolation from smallpox scabs. In addition, the facility at CDC had been commissioned to test the anti-viral activity of drugs using variola virus-infected cell cultures.

Analysis and sequencing of variola virus genomes

Data were presented on PCR-based RFLP analysis of orthopoxvirus DNA, a technique which may be used forensically for investigation of orthopoxvirus infections. Sequence analysis of Garcia-1966 strain of variola virus has been completed in both WHO collaborating laboratories as recommended by the report of the Ad Hoc Committee on Orthopoxvirus Infections, Geneva, 9 September 1994, but such results have not yet been published.

Biosecurity and physical security of WHO collaborating laboratories

The following recommendations have been made for laboratory containment of variola virus. Work with all remaining variola strains will continue to be carried out only in high containment biosafety level 4 laboratories (BSL4) at CDC, Atlanta, USA, and at VECTOR, Koltsovo, Novosibirsk Region, Russia, until international agreement on their destruction is reached. The laboratories will be subject to regular reviews by national safety authorities and to external review by WHO. Access to the material is strictly controlled and additional physical security measures to prevent removal of infectious material are in place.

Smallpox vaccine stocks and production

A global survey of smallpox vaccine and seed virus indicated there are approximately 60 million doses of smallpox vaccine available. There is little current smallpox vaccine manufacture but vaccine seed is available from the WHO Collaborating Centre for Smallpox Vaccine at the National Institute of Public Health and Environment, Bilthoven, The Netherlands.

Deliberate release of smallpox virus

A paper was presented on the risk of deliberate release of smallpox virus and its impact on virus destruction. Smallpox virus is considered to be the primary candidate for use as a biological weapon. The infectious dose is likely to be small and there is documented evidence of ready aerosol spread of the virus which is further supported by the viability of the virus under various environmental conditions of temperature and humidity. A 30% case-fatality rate can be predicted in non-vaccinated individuals exposed to smallpox and the potential for secondary spread could result in 10 secondary cases for each primary case. Hospital beds suitable for isolation of smallpox cases are available only in small numbers and it could take 3 years to achieve large-scale commercial production of smallpox vaccine. Bioweapons expertise and equipment for manufacture already exist that could be made available to terrorist organizations.

This assessment was taken into consideration when the Ad Hoc Committee deliberated upon destruction of variola virus stocks.

Survey of WHO Member States latest position on destruction of variola virus

Of 191 WHO Member States contacted in early 1998, 79 replies were received and 74 responses favored destruction of all variola virus stocks as indicated under Resolution WHA49.10. Four Member States were undecided and one was against destruction.

Recommendations

The 1999 Ad Hoc Committee on Orthopoxvirus Infections made the following recommendations:

(a) If destruction is confirmed

- National authorities that have contributed collections held at the two WHO collaborating centres should be advised of the plans to destroy the virus strains transferred to WHO repositories.
- The process set out in the 1994 report of the Ad Hoc Committee should be followed at the time of destruction of smallpox virus stocks. However, signatories to the certification of destruction should involve the Head of State instead of the "most senior health official" as originally proposed in that report.
- Stocks of smallpox virus-infected material in which the virus has been killed by γ-irradiation should be excluded from destruction. Such γ-irradiated, killed material should be produced before destruction of smallpox virus stocks but be safety-tested to ensure it does not contain live virus.
- WHO Member States should be asked to reconfirm that they do not have stocks of smallpox virus.

(b) If destruction is further delayed

- WHO should ensure regular visits (at least every five years) to the repositories of smallpox virus to review biosafety and security.

(c) In both cases

- It is important that clinical, epidemiological, laboratory and ecological features of the cases of rash illness in the areas associated with outbreaks of human monkeypox be investigated carefully and promptly.
- Stocks of archival cloned DNA should be kept in both WHO repositories and they should include duplicated stocks of two strains of variola major virus and one strain of variola minor virus.
- WHO should advise its Member States to retain their stocks of smallpox vaccine.
- The stockpile of the smallpox vaccine (Lister Elstree strain) stored in the National Institute of Public Health and Environment, Bilthoven, Netherlands, should be maintained and regularly checked.
- The deliberate release of smallpox virus should be considered a crime.