GLOBAL HEALTH SECURITY

EPIDEMIC ALERT & RESPONSE

WHO Advisory Committee on Variola Virus Research

Report of the Fifth Meeting

Geneva, Switzerland
4 - 5 November 2003

World Health Organization

Department of Communicable Disease Surveillance and Response

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Contents

Summary

The fifth meeting of the WHO Advisory Committee on Variola Virus Research reviewed current progress in essential research requiring access to live variola virus. Significant progress has been made during the past reporting year, particularly in the further characterization of the variola virus isolates held in the two repositories, on the development of diagnostic procedures for smallpox, and on studies of the genomic DNA diversity of variola virus. Additional progress was also reported on further refinement of the non-human primate model of smallpox and its use for assessing the efficacy of new antiviral compounds and vaccines.

The committee made the following recommendations:

- Chimeric viruses held in the Centers for Disease Control and Prevention (CDC) repository should be destroyed and removed from the inventory; this would not preclude the preparation of genomic DNA samples for subsequent archiving.

- Isolates shown to be non-viable using the procedures employed should be similarly destroyed and removed from the inventories, with DNA being isolated if considered useful for future studies.

- WHO should approach the responsible authorities of the collaborating centres to implement the recommendations concerning destruction of the virus isolates identified above.

- The virus inventories held by the two collaborating centres should be updated according to a standardized format set up in collaboration with the WHO secretariat. Progress on implementing this recommendation should be reviewed at the next meeting of the Advisory Committee.

- Non-variola virus orthopoxviruses held in the CDC repository should not appear on the inventory and should either be held separately within the BSL-4 facility or be destroyed, as recommended previously for isolates whose retention was not scientifically justified.

- Methodologies for all diagnostic assays for smallpox developed during this programme should be made available to Member States that request them.

- Additional research should be conducted to validate the current procedures for extraction of DNA from authentic clinical samples containing variola virus DNA and to validate the available diagnostic tests using material from variola virus-infected non-human primates or historical samples.

- Further work should be done using the primate model of human smallpox to facilitate the identification of candidate antiviral compounds and vaccines.

- Work on the characterization of potential antiviral lead compounds and on the development of new vaccines should be given a high priority.

- WHO should provide guidelines for assessing the quality, safety and efficacy of new generation smallpox vaccines for those Member States engaged in this important research.

- The recommendations of the technical sub-committee and the views of members of the Advisory Committee on the simultaneous handling of variola virus and other orthopoxviruses, on the genetic engineering of variola virus, on the expression of variola virus genes in other orthopoxviruses and on the distribution of variola virus DNA should be referred to WHO's Biosafety Advisory Group and, subsequently, to the Ad Hoc Committee on Orthopoxvirus Infections for final adjudication.

1. Introduction and report of the Secretariat

1.1 Dr Guénaël Rodier, WHO Director, Communicable Disease Surveillance and Response (CSR), welcomed participants to the meeting. He indicated that the purpose of the meeting was to review current progress on research using live variola virus, to comment on the essential research required in advance of further consideration of the destruction of all remaining known live virus stocks. Dr Peter Greenaway was appointed Chairman and Dr Robert Drillien Rapporteur.

1.2 Dr Cathy Roth then summarized the work of the WHO Advisory Committee Secretariat during the past year. A standard electronic format for recording the variola virus inventories held by the two WHO collaborating centres had been prepared and would soon be available for distribution. The information to be collected would include origin, history, virulence, titre, etc. of each of the isolates in the repositories and records on material used for work in progress. She indicated that inspections of the BSL-4 facilities within each of the two WHO collaborating centres had been completed.

1.3 A number of associated activities were then described. These included the potency testing of the smallpox vaccine reserve held by WHO (all stocks potent), the archiving of smallpox-related documents generated between 1987 and 1998 and the investigation of rumours of two possible smallpox cases (both negative). WHO had also organized workshops on the modelling of a smallpox outbreak, on virus isolation and case management, and on the laboratory validation of diagnostic assays. The Organization had also held a training course for those involved in the training of emergency responders to a smallpox outbreak and had participated in the international emergency response exercise known as "Global Mercury".

1.4 Some of these initiatives fell outside the remit of the Advisory Committee on Variola Virus Research and were more policy-related. It was therefore expected that the Ad Hoc Committee on Orthopoxvirus Infections would be reconvened to consider the policy-related initiatives and relevant recommendations of this Advisory Committee.

1.5 Dr Riccardo Wittek then described the work of the technical panel convened following the fourth meeting of this Advisory Committee. Members had been selected from the Advisory Committee on the basis of their scientific expertise and representation on national biosafety committees. The panel's draft recommendations were available for discussion later in the agenda.

2. Report and update on biosafety

2.1 Dr Nicoletta Previsani described aspects of the WHO Biosafety Programme relevant to variola virus. She indicated that the WHO Biosafety Programme had recently been joined by

the Emergency Preparedness Team. With respect to emergency preparedness, WHO had developed surveillance standards for smallpox and standard operating procedures for outbreak response procedures.

2.2 The revised regulations for the transport of infectious substances were described. These were now being considered by the international civil aviation authorities and the International Air Transport Association (IATA). The object is to seek harmonization of transport regulations between the airline and national authorities. These regulations were dependent on the categorization of infectious substances into those considered most dangerous (including variola virus) and those of low risk. A list of the agents in each category was distributed to Committee members.

2.3 During the ensuing discussion it was agreed that biosecurity, in addition to biosafety, would be an important consideration if the transportation of live variola virus were ever considered outside of an outbreak situation. It was noted that Congo 9 was the only common isolate held by the two collaborating centres and that at some point in the future the exchange of key samples might need to be contemplated. It was unclear who would be the ultimate authority to sanction such exchange if, indeed, it were ever considered practical.

3. Virus repositories

3.1 Progress reports on ongoing research with live variola virus were presented by scientists from the CDC and the Russian State Centre for Virology and Biotechnology (VECTOR) laboratories. The current variola virus stocks at CDC include 451 isolates, of which 49 have been selected for viability studies. Forty-five of these isolates could be propagated in tissue culture. Polymerase chain reaction/restriction fragment length polymorphism (PCR/RFLP) analysis of DNA samples from the 45 isolates has allowed the establishment of dendrograms that demonstrate the clustering of the isolates into clades according to the geographical origin of the viruses. Methods such as extended PCR/RFLP and capillary RFLP have been employed to identify more precisely the geographical origin of isolates of particular interest. Out of the 120 samples at VECTOR, 55 were tested for viability and 32 could be propagated. DNA from 21 isolates at VECTOR has been analysed by long PCR/RFLP analysis. This work has facilitated the construction of dendrograms that show the distribution of the isolates into three major groups (African, Asian and Alastrim virus). Analysis of Moscow isolates from the 1960 outbreak has identified polymorphic differences in the genomes of individual isolates.