Destruction of variola virus: Memorandum from a WHO meeting*

This Memorandum discusses the fate of variola virus stocks which have been kept in two WHO Collaborating Centres, as well as cloned DNA fragments of variola virus genome, smallpox vaccine, and seed vaccinia virus for the production of this vaccine. General and specific recommendations are given concerning destruction of variola virus; storage, distribution and handling of cloned DNA fragments of variola virus genome; and about stocks of smallpox vaccine.

The eradication of smallpox during the late 1970s is among the greatest public health achievements of all time. This success resulted from an unprecedented international effort coordinated by WHO and was recognized by the 33rd World Health Assembly which declared on 8 May 1980 the global eradication of smallpox.

Since the global eradication of smallpox, the stock of variola viruses has been gradually reduced and is now restricted to two WHO Collaborating Centres on Smallpox and other Poxvirus Infections, designated at the Centers for Disease Control and Prevention, Atlanta, GA, USA, and at the Institute for Viral Preparations, Moscow, Russian Federation.

The members of the Committee on Orthopoxvirus Infections, at a meeting in March 1986, unanimously recommended the destruction of the virus stocks kept in the two laboratories (1). In connection with this recommendation, the Committee noted that the variola gene pool could be cloned into non-expressing sites of bacterial plasmids for future studies of variola virus and that archival records of variola virus would be satisfied by such cloned DNA. The Committee also considered that the cloned DNA would provide sufficient reference material to resolve any future diagnostic problem involving suspected smallpox.

The meeting of the Ad Hoc Committee on Orthopoxvirus Infections in December 1990 confirmed the recommendation and proposed a deadline of 31 December 1993 for the destruction (2). The Committee recommended that, in the meantime, the complete nucleotide sequence of the genome of at least one variola virus strain should be determined. The Committee considered that the sequence information might represent a useful and potentially safer record than the cloned material for archival purposes.

The WHO Technical Committee on the Analysis of Nucleotide Sequences of Variola Virus Genomes reviewed the data obtained in the sequencing project at a meeting in January 1994. This Committee acknowledged that the information obtained in the project exceeded the minimum requested by WHO.

The publication of the Ad Hoc Committee’s recommendation to destroy the variola viruses had, however, triggered mixed reactions from both the public and the scientific community. Diverging views attracted the attention of the media and were the subject of letters received in WHO from concerned individuals. The question was therefore given a frank and open airing in a round-table discussion.

* This Memorandum is based on the report of a WHO meeting of the Ad Hoc Committee on Orthopoxvirus Infections held in Geneva on 9 September 1994. The participants at the meeting were: I. Arita (Kumamoto City, Japan); K. Banerjee (Pune, India); W. Dowdle (Atlanta, GA, USA); K. Dumbell (Cape Province, South Africa); J. Esposito (Atlanta, GA, USA); F. Fenner (Chairman) (Canberra City, Australia); P.J. Greenaway (Rappporter) (London, England); D.A. Henderson (Washington, DC, USA); B.W.J. Mahy (Atlanta, GA, USA); S.S. Marennikova (Koltsovo, Russian Federation); H.G. Schatzmayr (Rio de Janeiro, Brazil); WHO Secretariat: K. Esteves, Y. Ghendon, R.H. Henderson, L.J. Martinez, G. Torrigiani.

Requests for reprints of this article should be sent to Programme on Bacterial, Viral Diseases and Immunology, Division of Communicable Diseases, World Health Organization, 1211 Geneva 27, Switzerland. A French translation of this article will appear in a later issue of the Bulletin.
organized in August 1993 in conjunction with the IX International Congress of Virology in Glasgow, Scotland, where scientists representing the two opposing opinions were invited to make their views public.

Variola virus stocks

The Ad Hoc Committee, at its meeting on 9 September 1994, considered the arguments for and against the destruction of the variola virus stocks, which are summarized below.

Arguments against destruction:

- All possibility of future studies on the variola virus will be lost (properties of viral genes and proteins, biological functions of the virus, pathogenesis, etc).
- Destruction of the viruses in the two known repositories may not guarantee the complete removal of the virus from the Earth (preserved corpses of smallpox cases, forgotten or hidden stocks elsewhere).

It was suggested that destruction should be agreed in principle, but should be postponed to allow more time for further analysis of the sequenced genomes of variola virus and for weighing of scientific merits when further advances in methods and understanding had occurred.

Arguments for destruction:

- The escape of the variola virus from the laboratories would be a serious risk because an increasing proportion of the global population lacks immunity to the disease owing to cessation of vaccination and revaccination against smallpox more than 10 years ago.
- The sequence information and the availability of cloned DNA fragments of the full genome of several strains of variola virus allow most scientific questions about the properties of the viral genes and proteins to be resolved. The cloned DNA fragments of the virus genome are non-infectious and can be handled in safety.
- The decision to eradicate smallpox was a collective decision of the world community, based on public health considerations and all measures should be taken to ensure that smallpox does not again afflict mankind.

The members of the Ad Hoc Committee on Orthopoxvirus Infections discussed in detail the issues relating to the destruction of the last stocks of variola virus. They agreed that the scientific arguments for retention were clear and that there was some potential for learning more about the virus, its virulence and pathogenicity; not all desirable studies could be done with cloned virus DNA. The lack of a convenient laboratory animal and the need to work in high security (P4) facilities, however, limited the potential of such work. Those favouring early destruction of the virus indicated that many of the scientific questions raised could be better addressed by using other orthopoxviruses, or were of lower priority than a variety of issues pertaining to agents still causing widespread disease. It was noted that the scientific community had been consulted widely and that many supported destruction including the Executive Board of the International Union of Microbiological Societies, the Presidium of the Russian Academy of Medical Sciences, the Council of the American Microbiological Society, and the Board of Directors of the American Type Culture Collection.

The Committee unanimously agreed that all remaining stocks of variola virus should be destroyed, including whitepox virus, viral genomic DNA, clinical specimens and other materials containing infectious variola virus held in the WHO Collaborating Centres for Smallpox and other Poxvirus Infections in the Centers for Disease Control and Prevention, Atlanta, GA, USA, and in the Institute for Viral Preparations, Moscow, Russian Federation.

There was debate over the date on which destruction should occur. Those favouring early destruction considered that the genomic sequence data from several strains of variola virus, with the availability of other sequences cloned in bacterial plasmids, satisfied the need for an archival record of the virus. They noted that these cloned DNA fragments would provide sufficient reference material to resolve any future diagnostic problem involving suspected smallpox and allowed for future studies of properties of variola virus genes and proteins. They also stressed that escape of variola virus from the laboratory would be a serious risk to the increasing proportion of the population that lacks immunity to smallpox. They noted that the decision to eradicate smallpox was a collective decision of the world community, based on public health considerations, and health officials and others in many countries were concerned about the continued retention of stocks of variola virus, especially as some of these countries had made considerable efforts to destroy their own variola virus stocks.

Members of the Ad Hoc Committee in favour of postponing destruction of the virus recommended that the archival storage of variola virus be continued in the two Collaborating Centres. They considered that the rapid advances in science and technology now occurring would enable new questions to be addressed in the future and that it was therefore too
early to take this irrevocable step. They urged that serious consideration be given to storing the virus for
a further five years.

The majority (8/10) of the members of the Ad Hoc Committee on Orthopoxvirus Infections recom-

mended that the date for the destruction of the remaining stocks of variola virus and other materials as
listed above should be on Friday 30 June 1995 in both Centres, subject to agreement by the World
Health Assembly in May 1995.

Cloned DNA fragments of variola virus genome

The Ad Hoc Committee revised the recommendation of the last meeting about destruction of all recombi-
nant materials that contain variola virus DNA sequences. Taking into account that cloned DNA
fragments of variola virus genome are themselves not infectious and provide a useful resource and tool
for analysing variola virus genes and protein structure and function, the majority (9/10) of the members
of the Ad Hoc Committee recommended that such cloned material should be kept. The Committee also
recommended the establishment of two international repositories for the storage, maintenance, distribution
and monitoring of the cloned DNA fragments of variola virus genome — one at the WHO Collaborat-
ing Centre for Smallpox and Other Poxvirus Infections, Centers for Disease Control and Prevention,
Atlanta, GA, USA and the second at the Russian State Research Centre of Virology and Biotechnol-
yogy, Koltsovo, Novosibirsk Region, Russian Federation.

The Committee recommended that special measures should be adopted for the handling of cloned
DNA fragments of variola virus genome, as follows:

— All work with cloned DNA fragments containing variola virus genetic information (greater than
100 nucleotides long) should only be done following a written risk assessment and in accord-
ance with locally agreed national guidelines.

— The insertion of variola virus genome sequences into genetic material of other orthopoxviruses is
prohibited. No other orthopoxviruses should be handled in the laboratory rooms where material
containing cloned variola virus genome sequences are studied.

— All by-products containing cloned DNA fragments of variola virus genomes and other related
materials must be disposed of by autoclaving at 120 °C for 30 minutes.

Smallpox vaccine

The Ad Hoc Committee revised the recommendations of the fourth meeting of the Committee on
Orthopoxvirus Infections, which was held in 1986, regarding the elimination of the emergency stock of
smallpox vaccine and retention of the seed virus stock for preparation of the vaccine. The Committee
recommended that the 500,000 doses of smallpox vaccine, currently in storage at −20 °C at WHO,
should be retained indefinitely and be retested for potency every five years.

The Ad Hoc Committee recommended that the Lister Elstree strain of vaccinia virus should continue
to be kept as the smallpox vaccine seed virus stock. It was also recommended that the seed virus, in quan-
tities of about 3 litres, should be kept at −20 °C by the WHO Collaborating Centre for Smallpox Vac-
cine at the National Institute of Public Health and Environmental Protection, Bilthoven, Netherlands.

Recommendations

(1) The members of the Ad Hoc Committee unanimously recommended that all stocks of variola virus
should be destroyed by autoclaving followed by incineration, including all whitepox viruses, clinical spe-
cimens, and other materials containing infectious variola virus or viral genomic DNA, held in the
WHO Collaborating Centres for Smallpox and other Poxvirus Infections at the Centers for Disease
Control and Prevention, Atlanta, GA, USA, and the Moscow Institute for Viral Preparations, Moscow,
Russian Federation. Subject to agreement by the World Health Assembly, the majority view (8/10
members) was that destruction should occur in both Centres on Friday, 30 June 1995. A minority view
(2/10 members) was that destruction of variola virus stocks should be delayed for a maximum of five
years for scientific studies.

(2) Variola virus genomic DNA should be destroyed in all laboratories holding such material when the
variola viruses are destroyed in the Collaborating Centres for Smallpox and other Poxvirus Infections.

(3) The certificate signed by WHO Commission members attesting that the variola virus stocks have
been destroyed and the confirming statement of the Director of the Institute should be transmitted to the
World Health Organization by the most senior health official of the Russian Federation and the USA. The
certificate and the statement should be accompanied by an attestation, signed by that health official,
affirming that there in the country no known
remaining strains of variola virus, clinical specimens, or uncloned viral genomic DNA.

(4) The majority of the Ad Hoc Committee (9/10) recommended that stocks of cloned fragments of variola virus DNA should be retained. Two designated WHO International Repositories for the storage, maintenance, distribution and monitoring of the cloned DNA fragments of variola virus genome at the Centers for Disease Control and Prevention, Atlanta, GA, USA and at the Russian State Research Centre for Virology and Biotechnology, Koltsovo, Novosibirsk Region, Russian Federation should be established. Each repository should hold a duplicate set of archived material. Requests for access to these stocks should be made through WHO headquarters and the stocks should only be released under specified conditions which guarantee that they will be handled under nationally agreed guidelines. Work should not be done in laboratory rooms that are concurrently handling orthopoxviruses. Insertion of variola virus genome sequences into genetic material of other orthopoxviruses is prohibited.

(5) The Centers for Disease Control and Prevention, Atlanta, GA, USA should publish their detailed protocols for undertaking validated tests for differentiating variola major and Alastrim strains from each other and from other orthopoxviruses.

(6) A prioritized programme of work should be undertaken before 30 June 1995 to obtain certain additional DNA sequences, and to complete the cloning of DNA for the Garcia-1966 strain of variola virus. Sets of clones containing variola DNA sequences should be prepared and fully archived for distribution to the designated repositories. The Committee hopes that DNA sequences for other species of orthopoxviruses will be obtained by laboratories interested in poxvirus studies.

(7) A stock of smallpox vaccine (500,000 doses) should continue to be kept by WHO headquarters in case of emergency. This should be stored at -20 °C and retitrated every 5 years.

(8) Smallpox vaccine seed virus (vaccinia virus strain Lister Elstree) should continue to be kept at -20 °C by the WHO Collaborating Centre for Smallpox Vaccine at the National Institute for Public Health and Environmental Protection, Bilthoven, Netherlands. Seed virus should be tested every 5 years and, if necessary, additional passages of seed virus should be done at this Institute.

(9) These recommendations should be submitted for consideration at the 95th Executive Board meeting (January 1995) and at the 48th World Health Assembly (May 1995).

References