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WHO Advisory Committee on Variola Virus Research

Report of the Twelfth Meeting

Geneva, Switzerland
17–18 November 2010

GLOBAL ALERT AND RESPONSE

World Health Organization

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1. Report from the Secretariat

1.1. The WHO Advisory Committee on Variola Virus Research met on 17 and 18 November 2010 with Professor G.L. Smith as Chairman and Drs R. Drillien and F. McLellan as Rapporteurs.

1.2. Dr K. Fukuda opened the proceedings, noting that discussions on these issues have been ongoing since 1986 and remain of great interest to countries. Among other items for discussion, this group has been assembled to assess a major review of research related to variola virus, in advance of a discussion to take place at the Sixty-fourth World Health Assembly on the timing of the destruction of variola virus stocks. The assessment will consider two key items: firstly, a review of the literature and unpublished data conducted by a group of scientists endorsed by this committee; and secondly, an external review of the review itself, which has been conducted by experts outside the variola virus field. This meeting will produce a meeting report in addition to the other two documents, all of which would be made available as soon as possible prior to being submitted to the Executive Board in January 2011.

1.3 Dr P. Formenty updated the group on this year's activity in the WHO Smallpox Project. The report of last year's meeting of the Advisory Committee was noted by the World Health Assembly in May 2010. The report of this 12th meeting will be submitted to the Sixty-fourth World Health Assembly in May 2011. In May 2007, a major scientific review was called for in resolution 60.1; later in 2008 it was decided that this review would consist of two parts – the scientific review itself and an independent review of it by external experts outside the field of smallpox (the Advisory Group of Independent Experts to review the smallpox research programme, or AGIES, report). The inspection report of the WHO Collaborating Centre at Centers for Disease Control and Prevention, United States of America, was finalized last year and a report of the WHO Collaborating Centre at VECTOR (Novosibirsk, Russian Federation) is now being finalized. The work of the subcommittee on the Smallpox Laboratory Network has begun under the leadership of Dr J.-C. Piffarretti as coordinator. Standard Operating Procedures have been developed for the smallpox vaccine stockpile. The Archive project, which consists in part of scanning all the documentation related to smallpox, some 700 000 pages of searchable documents, was be presented later in the meeting.

1.4 In line with WHO policy all members, advisers and observers of the Advisory Committee have completed and signed a Declaration of Interests. Six experts have declared a potential conflict of interest in the subject matter of this meeting. No relevant conflict of interests has been declared by the other experts. The declared interest reported by Peter Biggins and Jean-Claude Piffaretti were assessed to be minimal and unlikely to affect, or to be reasonably perceived to affect, their judgment. Four experts declared interests that the Secretariat has determined should be disclosed.

- Dr Jacob Thorup Cohn stated that he is employed by Bavarian-Nordic, a leading Danish privately held biotech firm in the field of smallpox countermeasures (antivirals, vaccines).

- Dr Randall Lanier stated that he is employed by and owns stock in Chimerix which is involved in the development of a product that may serve as a biodefense countermeasure in the event of a smallpox release. Dr Lanier further indicated that Chimerix has provided funding for his travel and subsistence for attendance at the current Advisory Committee meeting.

- Dr Grant McFadden stated that he had acted as a consultant for SIGA Corporation concerning their application to the FDA for drug approval of the ST-246 as an antiviral against smallpox.

- Dr Robert Drillien indicated that he has been a consultant for Bavarian-Nordic, a company producing a smallpox vaccine and that he was consultant for French Army on smallpox vaccine.

2. Update on WHO-approved research proposals

2.1 Dr R. Drillien gave an update on research proposals submitted to WHO and approved by the scientific subcommittee between November 2009 and August 2010. He noted that all the approved proposals are continuations of ongoing projects, not new proposals. Details of the projects are summarized in Annex 1. He briefly reviewed each proposal. The Committee asked the Secretariat to prepare a list of all research projects that have been concluded.

3. Update on variola virus DNA clones held at NICD, South Africa

3.1 Professor R. Swanepoel gave an update on the variola virus DNA clones held at the National Institute for Communicable Diseases (NICD), which is the successor to the National Institute of Virology, South Africa. After the declaration by WHO of the eradication of smallpox in 1980, all variola virus national collections were to be stored in four repositories located in the USA, the USSR/Russian Federation, South Africa, and the United Kingdom. In 1982 the variola virus stocks held in the United Kingdom were transferred to the United States. An agreement was reached that South Africa would be given the clones of recombinant plasmids containing variola virus DNA fragments that had been prepared in the United Kingdom by Dr K.R. Dumbell in exchange for destroying their stock. On 9 December 1983 the variola virus stocks were destroyed in the presence of Dr Dumbell who had been appointed by WHO to witness the destruction. NICD then received the non-infectious DNA clones of recombinant plasmids. The clones, which have never been used, are currently held, as of October 2010 in storage inside the BSL4 facility at NICD. The South African Department of Health has now decided that clones of recombinant plasmids potentially useful in producing diagnostic reagents, and constituting no more than 20% of the genome of the virus should be retained. The rest of the clones should either be transferred to the CDC repository or destroyed under the

supervision of WHO. If the CDC repository already has duplicates of the clones it would be better to destroy them in South Africa than to transport them.

COMMITTEE DISCUSSION: The Committee suggested that in the event that clones of recombinant plasmids containing variola virus DNA fragments are duplicated at CDC, there is no need for transfer of the stocks, nor for their retention.

4. Scientific Review of Variola Virus Research 1999–2010

4.1 The Chair thanked the authors of the Scientific Review of Variola Virus Research 1999–2010 for their work, and especially for their patience with editorial changes.

4.2 The overall assessment of the Committee was the following: the consensus view of the Committee on the conclusions reached in the review overall was that laudable progress has been made in all areas, while recognizing that additional science can be done. The past decade has seen a remarkable amount of output. Progress towards the goals for which the research was permitted has been exceptional but is not yet complete. The tasks for which live virus is needed have narrowed considerably.

4.3 Dr A. Alcami presented Chapter 1, on smallpox vaccines, which is summarized in Annex 1. The chapter concluded that "licensure of smallpox vaccines grown in tissue culture has been a useful step forward; however, use of these vaccines would be medically contraindicated for individuals with immunodeficiency and certain dermatological conditions. Since smallpox has been eradicated, the efficacy of new generation vaccines will need to be tested using poxviruses related to variola virus in animal protection studies, and safety and immunogenicity studies in humans. However, confidence in the ability of these vaccines to protect against smallpox would be increased by use of live variola virus for in vitro neutralization tests and non-human primate studies."

COMMITTEE DISCUSSION: The Committee recalled that the smallpox vaccine was essential for the eradication of smallpox. Nevertheless, there remains a compelling need for vaccines with a better safety profile. Some progress has been made along these lines: for example, a vaccine grown in tissue culture to modern standards of good manufacturing practice and an attenuated vaccine have been produced and licensed, and more attenuated vaccinia virus vaccine strains are in