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WHO Advisory Committee on Variola Virus Research

Report of the Eleventh Meeting

Geneva, Switzerland
4–5 November 2009

GLOBAL ALERT AND RESPONSE

World Health Organization

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Executive summary

The major accomplishments in the WHO variola virus programme were as follows:

- WHO smallpox vaccine emergency stockpile of 32.6 million doses was established, well in excess of the original target of five million. Four individual Member States have pledged 27 million doses to be given in case of additional needs.

- In light of the 2011 review process on smallpox research, the Committee had agreed that it would produce a report based on a series of reviews and these would be submitted to an external committee that was independent of both WHO and its Advisory Committee for review. The Advisory Committee considered and discussed six preliminary reviews.

- The potential usefulness of wild-caught prairie dogs (*Cynomys ludovicianus*) as a model for human smallpox was investigated. Because of the lack of overt illness, the prairie dog was not considered to be a good animal model for variola virus infections.

- Work continues in investigating protein-based diagnostics and the development of point-of-care assays that are simple to use, stable, robust and easy to interpret.

- The potential reservoirs of, diagnostics for, and the epidemiology of cowpox virus infections in Germany was reported, but cases have been reported in other European countries as well. Human infections through zoonotic transmission have been documented. It is believed that rodents are the reservoir. It was noted that the cowpox virus infections in rats may be a promising model of orthopoxvirus pathogenesis.

- The Committee was presented with a comprehensive review of antiviral agents which have shown anti-variola virus activity (cidofovir, ST-246 and CMX001). These compounds have obtained Investigational New Drug (IND) status from the US Food and Drug Administration (FDA). The Committee recalled that capability to perform work with live variola virus must be maintained at least until two anti-variola drugs with different mechanisms of action have gained regulatory approval.

- The access and preservation of the WHO archives of the Smallpox Eradication Programme was discussed. Work is under way to convert all the materials into a digital format which will allow full text searching.

- The Committee reviewed the risks and benefits of vaccinating with smallpox vaccine health-care workers exposed to monkeypox. The Committee decided that vaccination of health-care workers should be given to HIV negative health-care workers because of the risks associated with exposure to monkeypox virus. Vaccination after an outbreak was detected would not provide time for screening for HIV and would be too slow to offer optimal protection.

Content

1. Report from the Secretariat

1.1. The WHO Advisory Committee on Variola Virus Research met on 4 and 5 November 2009 with Professor G.L. Smith as Chairman and Mr D.W. FitzSimons as Rapporteur.

1.2. Dr K. Fukuda opened the proceedings, recalling the importance of the eradication of smallpox for current work on the eradication of other diseases. He outlined the process for responding to the request of the Health Assembly in resolution WHA60.1.

1.3. Dr D. Lavanchy recalled that the report of the tenth meeting had been noted by the Sixty-second World Health Assembly in May 2009.[1] He reported on the successful inspection of the smallpox repository and containment facilities at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, United States of America, in March 2009 and indicated that, for the first time, the report is publicly available on the WHO web site.[2] The inspection of the smallpox repository and containment facilities at the VECTOR laboratory in Novosibirsk, Russian Federation, is scheduled for December 2009.

1.4. A WHO smallpox vaccine emergency stockpile is stored securely in Switzerland; it includes 32.6 million doses, well in excess of the original target of five million. Potency testing is currently being conducted at the National Institute of Virology in the Netherlands. Donations to the stockpile are still welcome, including newer generation vaccines, bifurcated needles and other materials. Standard operating procedures for release and distribution of this stockpile have been prepared. Four individual Member States have pledged 27 million doses to be given in case of additional needs, and similar standard operating procedures are being drafted with these four Member States. The ad hoc Committee on Orthopoxvirus Infections recommended an emergency stockpile of 200 million doses.

1.5. Later in the course of the meeting Dr D. Lavanchy proposed new members for the Committee's scientific subcommittee, which the Committee approved.

2. Institute of Medicine report

2.1. Dr D. Ulaeto presented a brief overview of the report from the United States National Academy of Sciences Institute of Medicine's Committee on the Assessment of Future Research Needs for Live Variola Virus,[3] in the preparation of which he was the only representative of the WHO Advisory Committee to participate. The report was released simultaneously with the Advisory Committee's meeting. The Institute's Committee concluded that live variola virus was required for the development of therapeutics and assessment of resistance to these drugs and for the development of vaccines that do not manifest a "take". As the only known reservoir of variola virus is man, it recommended that CDC undertake a comprehensive evaluation of the work done to date on the non-human primate model of variola pathogenesis, in conjunction with an expert panel knowledgeable about poxviruses and animal models of viral infection. The objective

[1] Document WHA62/2009/REC/3, summary record of the fourth meeting of Committee B, section 2B.
[2] http://www.who.int/entity/csr/disease/smallpox/Report_2009_CDC_WHO_Inspection.pdf
[3] IOM, Live Variola Virus: considerations for continuing research: http://www.iom.edu/en/Reports/2009/LiveVariolaVirusContinuingResearch.aspx

would be to identify ways in which the predictive value of the model for testing therapeutics and vaccines might be improved. It stated that further genome sequence analysis would be useful but was not essential. It also recommended to explore the use of functional genomics in order to improve understanding of the origin and development of variola virus and to advance the development of new strategies for safe and effective therapy.

2.2. The Chairman recalled that the Advisory Committee had repeatedly agreed that further sequencing was not justified for public health. As the Advisory Committee is undertaking a comprehensive review of variola virus research and the resulting report will be reviewed by an independent panel of experts, the Advisory Committee will evaluate at its next meeting whether further evaluation of the non-human primate model of variola virus infection is deemed appropriate.

3. Update on research proposals

3.1. Dr R. Drillien reported that in the course of 2009 seven new proposals for research had been received, three from CDC and four from VECTOR (the latter submitted to the subcommittee only recently). The CDC proposals were approved for one year and covered protein-based diagnosis, diagnostic materials and assays for less reactogenic vaccines.

4. Review papers

4.1. The Committee had previously agreed that it would produce a report based on a series of reviews and Dr D. Lavanchy outlined the process for reviewing manuscripts prepared by Committee members for that purpose. That report would be submitted to an external committee that was independent of both WHO and its Advisory Committee for review and assessment of the achievements made over the past 10 years, identification of gaps that remain, and determination of the outcomes for public health. The composition and membership of the external committee were being decided. The Advisory Committee considered and discussed the following six reviews.

4.2. Dr I. Damon summarized the detailed information that had been collated on the status of the collection of strains of virus and nucleic acid samples in both the American and Russian repositories (CDC and VECTOR). The Committee suggested harmonization of the presentation of the data and that more precise quantitative information should be provided to the Committee.

4.3. Dr Damon also introduced a further collaborative review of laboratory diagnosis of smallpox and variola virus, covering aspects of clinical signs and symptoms, collection and handling of specimens, and the range of methods used. These methods included electron microscopy, virus isolation, DNA-based methods (e.g. restriction fragment length polymorphism, polymerase chain reaction-based approaches, and oligonucleotide microarray assays), sequencing, protein-based assays and serological antibody tests. One suitable test kit is commercially available for research purposes only, but is not licensed for diagnosis. In discussion, concern was expressed about the lack of broad access to licensed diagnostic tests in most Member States. A possible role

for WHO would be to investigate the pre-qualification procedures.[4] The core capacities required under the International Health Regulations (2005) might be a lever for increasing availability of diagnostic test kits.

4.4. Dr G. McFadden presented a multi-author review of variola genomics, covering the sequencing of 49 variola virus strains (the data have been published in the public domain), [5] the virus's evolution over time, poxvirus genome technologies, and considerations for the containment of variola virus genomes. He noted that sequencing had not included the very short terminal hairpin sequences of the genome, but it was thought that knowledge of these noncoding sequences, which are similar to those of other orthopoxvirus terminal hairpins, was not essential. He highlighted the major and rapid advances made over the past 10 years in the technologies of viral genome sequencing, synthesis and informatics, and concluded that the synthesis of full-length variola virus genomes and the creation of live orthopoxviruses is now technically feasible. Because WHO's current approach to control of variola virus is based on restriction of live variola virus to only the two WHO reference laboratories and control of distribution of individual genes such that no laboratory has more than 20% of the variola genome, the development of new and simple synthetic technology will in the future no longer assure that full-length variola virus genomes could only exist in the two WHO reference labs. Members of the Committee stressed that Member States need to be aware of these advances in synthetic biology and their implications, in particular the need to review policies on biocontainment. These advances necessitate the continued evaluation of existing guidelines on work with live variola virus and variola virus DNA. Ethics and biosafety committees should be aware of, and responsible for, implementing guidelines at the local level. Even if poxvirus genome synthesis projects were to be undertaken, their application to the creation of a synthetic variola virus is prohibited by existing regulations and would be considered a crime against humanity.

4.5. Dr A. Alcami presented the joint review on vaccines against smallpox, from the history of vaccination, the origin of vaccinia virus and the WHO Smallpox Global Eradication Programme. He went through the different generations of vaccines, from the first-generation vaccines generated in live animals, through second-generation vaccines produced in tissue culture and third-generation vaccines produced in tissue culture and characterized by attenuating mutations occurring during cell culture passage, to fourth-generation vaccines produced by genetic engineering technology. It was emphasized that first- and second-generation vaccines were licensed and highly effective, the first-generation vaccines having been used in the eradication of smallpox. The review also considered vaccination after exposure to smallpox before outlining the future