World Health Organization

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Smallpox eradication: destruction of variola virus stocks

Report by the Secretariat

1. Since the previous report,[1] the WHO Biosafety Inspection Team visited the biosafety level 4 laboratory at the Centers for Disease Control and Prevention in the United States of America in March 2009 and found the facility safe and secure for work with live variola virus. The report is available on the WHO web site.[2] The inspection of the Vector laboratory in the Russian Federation took place in December 2009.

2. This document reports on the eleventh meeting of the WHO Advisory Committee on Variola Virus Research (Geneva, 4 and 5 November 2009).

Update on vaccine stockpiles

3. A WHO smallpox vaccine emergency stockpile of 32.6 million doses is stored safely and securely in Switzerland. Donations to the stockpile, including third-generation vaccines, complete with bifurcated needles and other materials, are still welcome. Standard operating procedures for the dispatch of this stockpile have been prepared. Four individual Member States have pledged another 27 million doses to be given to WHO in case of additional needs and are working with the Secretariat on standard operating procedures for their dispatch. The Ad Hoc Committee on Orthopoxvirus Infections recommended that the WHO stockpile and that the Member States' pledges should reach a total of 200 million doses.[3]

Institute of Medicine report

4. In the United States of America, the Institute of Medicine's Committee on the Assessment of Future Scientific Needs for Live Variola Virus reviewed research since 1999, focusing on the use of live virus.[4] It concluded that live variola virus was required for the development and licensing of therapeutics and assessment of resistance, and for the development of vaccines that do not manifest a

[1] Document A62/23.

[2] http://www.who.int/csr/disease/smallpox/Report_2009_CDC_WHO_Inspection.pdf.

[3] Document WHO/CDS/CSR/ARO/2004.3.

[4] Arvin AM, Patel DM (eds), Institute of Medicine, Committee on the Assessment of Future Scientific Needs for Live Variola Virus. *Live variola virus: considerations for continuing research*. Washington DC, National Academies Press, 2009.

"take". It also made recommendations for the complete genome sequencing of all currently retained isolates in both repositories. The Chairman of the WHO Advisory Committee, however, recalled that the Committee had repeatedly agreed that further sequencing was not justified from a public health perspective.

Update on research proposals

5. During 2009 seven new proposals for research had been received: three from the Centers for Disease Control and Prevention and four from the Vector centre (submitted only recently). The first three proposals, on protein-based diagnosis, diagnostic materials and assays for less reactogenic vaccines, have been approved for one year.

Review process

6. The first step in the major review in 2010 requested in resolution WHA60.1 has been completed with the submission of six reviews of the literature and unpublished data arising from the research performed over the past 10 years. The six reviews covered the following topics:

- detailed information on the status of the collection of strains of virus and nucleic acid samples in both the American and Russian repositories
- laboratory diagnosis of smallpox and variola virus
- variola genomics, covering the sequencing of 49 variola virus strains
- vaccines against smallpox
- antiviral agents with anti-variola virus activity
- animal models and pathogenesis; experiments which have shown the efficacy of candidate vaccines and antiviral agents.

7. When compiled, the reviews will be submitted to a committee of independent experts appointed by the Director-General for review and assessment of the achievements made over the past 10 years, identification of any gaps which remain, and determination of the outcomes for public health. This will then be submitted to the Advisory Committee on Variola Virus Research for consideration and additional comment.

8. The final report will be submitted to the Executive Board for consideration at its session in January 2011; that report, and the Board's comments, would be further considered by the Sixty-fourth World Health Assembly in May 2011.

9. In discussion, concern was expressed about the lack of broad access to diagnostic materials and the unavailability of kits for diagnosis. A possible role for WHO would be to look into procedures for prequalification. The basic core capacities required under the International Health Regulations (2005) might be a lever for increasing availability of materials and kits.

10. Members of the Advisory Committee also stressed that Member States need to be aware of recent advances in synthetic biology, which now make it possible to synthesize a full-length variola virus genome. In resolution WHA52.10 the Health Assembly mandated that only the two WHO-

approved repositories may hold stocks of variola virus, but this approach needs review as it no longer ensures that full-length variola genomes exist in the two repositories only. These advances also 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, the creation of a synthetic variola virus is prohibited by existing regulations.

11. Members of the Advisory Committee emphasized that first- and second-generation vaccines were licensed and highly effective, the first-generation vaccines having been used in the elimination of smallpox. They noted that several promising candidate vaccines with fewer vaccination adverse effects were under development but not yet licensed. They noted that safety of newer vaccine candidates is relatively easy to show in human trials but efficacy is not.

Updates on WHO-approved research proposals

12. The Advisory Committee was informed about an investigation into the potential usefulness of wild-caught prairie dogs (*Cynomus ludovicanus*) as a model for human smallpox. Tests indicated, however, that the prairie dog was not a good animal model for variola virus infections.

13. Work on the development of protein-based diagnostics had detected a difference in sensitivity of an antigen-capture enzyme-linked immunosorbent assay to gamma-irradiated antigen and live variola virus antigen. Further work will be proposed in order to develop point-of-care assays that are simple to use, stable, robust and easy to interpret. Real-time polymerase chain reaction-based assays have been shown to have a specificity of 100% and a sensitivity of detection of five virus genome copies. A kit for inactivating variola virus for DNA extraction was validated, with complete inactivation achieved rapidly.

14. Research on the development of less reactogenic third-generation vaccines focused on the neutralization capacity of a modified vaccinia Ankara (MVA) vaccine. The MVA vaccine candidate had shown its ability to induce, after two-dose inoculation, an anti-variola neutralization response comparable to the Dryvax® first generation vaccine. Work is continuing to assess analytical methods to improve the evaluation of efficacy.

15. Data were reported on the collection of variola stocks in the two repositories. The collection at the Centers for Disease Control and Prevention holds 451 isolates and specimens as repository stocks, with no withdrawals or additions in the past year. It also contains working stocks, from which there have been 23 withdrawals for work on six WHO-approved protocols.

16. The variola virus collection at the Vector centre holds at present 120 strains. The repository also contains variola virus DNA: 199 vials containing full-length variola virus genome DNAs from 39 different variola virus strains; 1446 vials, comprising 17 individual collections of amplicons with variola virus DNA fragments; and 3795 vials comprising 16 individual collections of recombinant plasmids with variola virus DNA fragments. No additions or withdrawals were made in the last year.

17. Research into potential new therapeutic agents using live variola virus was reported, in particular inhibitors of protein tyrosine kinases. The WHO-approved research has shown that these inhibitors prevent the release of variola and monkeypox viruses from infected cells.

18. The development of CMX001 for treatment of smallpox was reported. Compared with cidofovir, CMX001 has greater in vitro activity against double-stranded DNA viruses (including

variola virus), is orally bioavailable, has no nephrotoxicity and is well tolerated in Phase I trials. Numerous animal studies have shown efficacy against other orthopox viruses. It has been used in one patient with generalized vaccinia infection following smallpox vaccination, but no efficacy conclusions can be drawn because the patient was receiving multiple antiviral treatments.

19. Research on the development of ST-246 has confirmed the drug's potency, lack of toxicity and specificity. It has proven effective in multiple animal studies and is orally bioavailable. It has been tested in Phase I clinical trials and is now in Phase II safety trials. ST-246 has been given Investigational New Drug approval and fast-track status in the United States of America. It does not interfere with immunization with either ACAM2000 or MVA vaccines in non-human primates and may therefore be considered to be given together with vaccines for vaccination of immunosuppressed individuals.

20. The Advisory Committee was updated on the attenuated smallpox vaccine LC16m8 (a third-generation vaccine), which is licensed in Japan and currently being stockpiled there as a precaution against bioterrorist attack. The vaccine is simple to administer, with a single dose using a bifurcated needle. National capacity for vaccine production is 80 million doses a year. Since the report to the Committee last year, work has continued on comparing the safety profile of the vaccine with that of Dryvax® in immunocompromised macaques, with no evidence of adverse reactions. A study of 267 subjects has shown that the vaccine is well-tolerated, with no serious vaccine-related adverse effects (including in allergic subjects) and good immunogenicity.

21. The Committee also heard the findings of a review of third-generation vaccines currently being examined in clinical studies, particularly MVA and LC16m8, in order to form the basis for guidance to WHO on acquiring a stockpile of such vaccines. Discussions stressed the importance of both these third-generation vaccines, which were considered to have fewer complications than previous generation vaccines. It was suggested that for pre-event vaccination MVA could be preferred because of the existing large body of data on its safety but in an outbreak situation the use of both LC16m8 and MVA could be considered.

22. The Committee was informed of the issues relating to the preservation of the archives of the Smallpox Eradication Programme. Their physical state is poor, and access for researchers is limited. A programme is under way to convert all the materials into a digital format which will allow full text searching and to restore the archives in order to ensure their longevity. The Committee warmly welcomed this approach, and was informed that a similar project had captured comparable material collected by the Centers for Disease Control and Prevention.[1]

23. The proposal submitted to the Committee last year for a smallpox laboratory diagnostic network[2] has been further elaborated. The network would comprise the two existing repositories and regional laboratories (the number of which needs to be determined, but possibly one per WHO Region). For the characteristics of the regional laboratories, an algorithm for processing suspicious samples and the required stringent criteria were outlined. In some regions transport of samples would be a problem (including air transport regulations as well as logistics). Suggestions were made to integrate the proposal into broader initiatives, for instance related to the International Health Regulations (2005) or WHO's programmes on laboratory capacity building and networking. The Committee recommended the formation of a subcommittee, to include at least one member from both

[1] http://www.globalhealthchronicles.org/.

[2] Document EB124/33 Add.2, paragraph 13.

WHO Collaborating Centres in order to set up a process to identify the appropriate local and regional laboratories.

24. The Committee also heard reports on potential reservoirs of, and diagnostics for, cowpox virus (which has been zoonotically transmitted to humans), and on the epidemiology of cowpox virus infections in Germany. (Cases have been reported also in other European countries.) It also was updated on the risks and benefits of vaccinating health-care workers exposed to monkeypox with smallpox vaccine.

ACTION BY THE EXECUTIVE BOARD

25. The Board is invited to note the report.

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