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WHO Advisory Committee on Variola Virus Research

Report of the Eighteenth Meeting

Geneva, Switzerland

2–3 November 2016

INFECTIOUS HAZARD MANAGEMENT

World Health Organization

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Executive Summary

The Advisory Committee on Variola Virus Research (ACVVR) held its Eighteenth meeting on 2 and 3 November 2016 at WHO Headquarters in Geneva.

ACVVR functioning
As requested by the 69th World Health Assembly in May 2016, the Advisory Committee's Terms of Reference have been refreshed and the membership has been expanded to include new members including those with specific expertise in synthetic biology and public health preparedness.

The Advisory Committee reviewed the implications for its upcoming work in light of the 69th World Health Assembly's decision to have a substantive agenda item at the 72nd World Health Assembly in May 2019 on the destruction of smallpox virus stocks. The Advisory Committee is expected to address research priorities in the interim period cognizant that the risk of smallpox re-emergence has increased as a result of the advent of synthetic biology technologies.

Reports on the virus collections
The Advisory Committee received reports on the virus collections held at the two WHO Collaborating Centres that are authorized as repositories of variola virus: the State Research Centre for Virology and Biotechnology (VECTOR), Koltsovo, Novosibirsk Region, Russian Federation, and the US Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, United States of America (USA).

Update on research
The Advisory Committee was updated on continuing research projects using live variola virus for the development of diagnostic tests, animal models, smallpox vaccines, and antiviral and therapeutic agents. Five research projects were deemed "essential public health research" using live variola virus and therefore approved in 2016 out of eight submitted.

Participants from CDC reported to the Advisory Committee on progress and challenges in the development of humanized mouse models for use in testing variola virus treatments. It was noted that CDC's research to validate a variola virus specific lateral flow assay (a diagnostic tool) was progressing, as were efforts to produce monoclonal antibodies as a possible therapeutic treatment strategy. CDC also described continuing research on the neutralizing capacity of two third generation vaccines, IMVAMUNE and LC16m8. VECTOR did not conduct research for much of 2016 due to scheduled shutdowns for decontamination and maintenance and for licensure and biennial biosafety inspections. However, in 2016 the Russian Federation had approved the use of a Russian-developed PCR multiplex real-time orthopoxvirus test kit for clinical use within the Russian Federation.

Progress was reported by the manufacturer on the development of IMVANEX/ IMVAMUNE. Although the vaccine's phase three clinical trial was still on going, the company planned to initiate new research into the vaccine's potential use as a treatment for monkeypox in high risk populations.

The manufacturer of TPOXX (Arestyr®/ ST-246), one of two antiviral treatments under development, reported that the product was edging closer to licensure. Efficacy and pharmacokinetic studies in animals had been successfully completed and all other required studies were underway for licensure application that was being prepared. Rabbitpox model studies in Brincidofovir (CMX001), a second antiviral being investigated as a treatment for smallpox, had been completed. Studies in the ectromelia model were ongoing.

The Advisory Committee also received a report from the US Food and Drug Administration on progress toward completing the studies required for the approval of various vaccines, diagnostic tests, and therapeutic medications for use with smallpox. No clear dates were provided for licensure.

The Advisory Committee was also presented with the results of orthopoxvirus research using synthetic biology. One study used bioinformatic phylogenetics to analyse the oldest known variola virus found in a Seventeenth century mummy. The other investigation described the synthesis of a horsepox virus using available commercial biotechnology.

Repository biosafety inspections

The WHO Smallpox Secretariat reported on the status of the biosafety inspection visits for the two smallpox repositories. For the current round, VECTOR's biennial biosafety inspection was completed in 2016, and CDC's was slated for May 2017.

Recommendations and observations

- The Advisory Committee strongly concurred with the Independent Advisory Group's assessment in its 2015 report on the Public Health Implications of Synthetic Biology Technology Related to Smallpox, namely that "*there will always be the potential to recreate variola virus and therefore the risk of smallpox happening again can never be eradicated*." The Advisory Committee noted that the advent of synthetic biology means that individuals can now create viruses such as variola, given information that exists in the public domain, and thus the threat that the virus poses to public health will not be eliminated by simply destroying the virus stocks housed in the two global repositories.
- The Advisory Committee strongly recommended that definition and implementation of policy that enhanced preparedness for a possible future smallpox event was highly desirable, especially in the context of the above mentioned capabilities engendered by advances in synthetic biology. They noted, in particular, the importance of point-of-care diagnostic tests as critical in detection of disease and thereby mitigating potential mortality and morbidity. There was consensus on pursuing a research agenda that will ensure point-of-care, generic and sensitive orthopoxvirus diagnostics in the near term. The Advisory Committee acknowledged the important work that both Collaborating Centres have already done to date on developing such diagnostics.
- Advisory Committee Members retained their prior recommendation for use of live variola virus in the development of antiviral drugs. It was observed that two compounds TPOXX® and Brincidofovir were in the final stages of work in their applications for licensure. While