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WHO Advisory Committee on Variola Virus Research

Report of the Nineteenth Meeting

Geneva, Switzerland

1 and 2 November 2017

INFECTIOUS HAZARD MANAGEMENT

World Health Organization

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Executive summary

The Advisory Committee on Variola Virus Research held its nineteenth meeting in Geneva on 1 and 2 November 2017. It considered the implications of its discussions in light of the upcoming substantive agenda item at the Seventy-second World Health Assembly in May 2019 on the destruction of variola virus stocks. Only one year remained for the Advisory Committee to draw conclusions from the outcomes of on-going research which would form the basis of its unequivocal advice to the Director-General about the current status of variola virus research.

WHO Smallpox Secretariat
The WHO Smallpox Secretariat outlined the reporting process to WHO's governing bodies over the next two years and the implications for the Advisory Committee's work. It also reported on recent developments including outbreaks of monkeypox, an emerging orthopoxvirus, in Africa. The link between variola virus research work and the prevention and control of monkeypox was noted and appreciated.

An update was presented on WHO's Smallpox Vaccine Emergency Stockpile and the Smallpox Vaccine Operational Framework which would be activated in the event of a smallpox event. WHO's work on the use of experimental vaccines and assessment of smallpox vaccines was outlined.

WHO's biosafety inspection team completed the current cycle of visits to the two authorized repositories of variola virus: the State Research Centre for Virology and Biotechnology (VECTOR), Koltsovo, Novosibirsk Region, Russian Federation in October 2016 and the US Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, United States of America (USA) in May 2017. The reports have been finalized and are available on the page of the WHO Smallpox Secretariat on the WHO website.

Reports on the collections of variola virus
The Advisory Committee received reports on the virus collections held at the two repositories, both WHO Collaborating Centres. In the past year, no withdrawals or additions had been made to either collection, and no genetic material had been transferred to other laboratories.

Update on research proposals
Six proposals for continuing research using live variola virus had been received from the two Collaborating Centres in 2017 (five from CDC and one from VECTOR), of which five had been (all from CDC) accepted as being of essential public health benefit.

Update on on-going research projects
The Advisory Committee was updated on progress in approved, continuing research projects using live variola virus for the development of diagnostic tests, animal models, smallpox vaccines, and antiviral and therapeutic agents, on work in the private sector on smallpox vaccine and antiviral agents, and regulatory perspectives.

Participants from CDC reported to the Advisory Committee on advances in protein-based diagnostic tests, which offered good prospects for the development of point-of-care tests. Work included preparation and use of human monoclonal antibodies, variola virus-specific antigen capture assays, lateral flow assays and protein microarrays. CDC's advisors also described work on real-time PCR-based diagnostics. One such assay was licensed by the Food and Drug Administration (FDA) in the USA in early 2017. Further work is focusing on an assay to detect all known pathogenic human orthopoxviruses. CDC also reported results of work on humanized mice as a model for smallpox and on the use of live variola virus in developing less-reactogenic, third-generation smallpox vaccines. The need for a better understanding of humoral responses and correlates of infection was identified.

Participants from VECTOR described progress in developing a vaccine from a recombinant strain of vaccinia virus that is less reactogenic and neurovirulent as well as more immunogenic and protective

than the vaccine derived from the parent strain. Preclinical studies are in progress. Researchers at VECTOR also used viral sequencing to establish the phylogeny of strains of variola virus isolated from patients during an outbreak of smallpox in Moscow in 1960, showing the high stability of the virus during the outbreak.

Update on progress towards licensure of antivirals and vaccines

The manufacturer of tecovirimat informed the Advisory Committee that all the necessary studies for regulatory approval of its oral formulation had been completed and submission of an application was in preparation, with a decision hoped for in the third quarter of 2018. The company was working with FDA towards submission for regulatory approval of an intravenous formulation.

The Advisory Committee was also updated about the development of brincidofovir, a second antiviral agent being considered as a treatment for smallpox but which is also used to treat patients infected with other double-stranded DNA viruses such as cytomegalovirus and adenovirus. Those studies have shown that the antiviral has acceptable safety and tolerability.

The manufacturer of the non-replicating MVA-based smallpox vaccine Imvamune®/Imvanex® reported that regulatory studies in preparation for an application for FDA approval were under way. The aim was to submit an application in the second half of 2018.

The Advisory Committee was updated on FDA's perspectives on the development and approval of smallpox countermeasures, including the evolution of its Animal Rule and the giving of Pre-Emergency Use Authorization for Imvamune®.

Recommendations and observations

Diagnostics

The Advisory Committee welcomed FDA's licensing of a new variola virus-specific, real-time PCR diagnostic test, and its availability to laboratories that are members of the US Laboratory Response Network. It also welcomed the considerable progress that has been made in the development of protein-based diagnostic tests and the prospects for their use in the field. Members of the Advisory Committee were divided on whether the use of live variola virus for their further development of diagnostics would be considered as "essential for public health".

Antiviral agents

The Advisory Committee appreciated the updates on potential therapeutic agents against smallpox, tecovirimat and brincidofovir, and welcomed the likely imminent submission of an application for licensure of tecovirimat to FDA. It noted that at least 24 months' more work was needed before an application for licensure of brincidofovir for use against variola virus was likely. It was encouraged by early results on the use of a combination of human monoclonal antibodies to neutralize variola virus.