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WHO Advisory Committee on Variola Virus Research

Report of the Seventeenth Meeting

Geneva, Switzerland

12–13 January 2016

PANDEMIC AND EPIDEMIC DISEASES

World Health Organization

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Executive Summary

The Advisory Committee on Variola Virus Research held it Seventeenth meeting on 12 and 13 January 2016 at WHO headquarters in Geneva.

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 Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, United States of America (USA).

It was also provided with updates on the continuing research projects using live variola virus for the development of diagnostic tests, animal models, smallpox vaccines, and antiviral and therapeutic agents. As concluded in the Fifteenth meeting of the Advisory Committee (24 and 25 September 2013), the only new projects to be approved were for antiviral agents against smallpox. The Advisory Committee discussed the estimated timelines for the ongoing research projects and expected that the completion and final review of these projects will take a minimum of three years. Of the proposals for research submitted in 2014-2015 that involved live variola virus the Advisory Committee's Scientific Subcommittee approved three from Vector (all extensions of existing projects) and five from CDC (four extensions and one new project).

Participants from CDC reported advances in the area of diagnostics, including the preparation and use of monoclonal antibody mixtures in diagnostic assays for viral particles or antigen capture, and variola virus proteome chips for profiling antibody responses. Work is also under way to investigate immune responses including duration of immune memory and viral neutralization. At Vector, an investigational new live smallpox vaccine was shown to induce neutralizing activity equivalent to that induced by conventional vaccines.

Progress was reported on the development of tecovirimat, one million treatment courses of which have been added to the US Strategic National Stockpile. Additional human safety studies are planned. Studies of brincidofovir, which is also in development for the treatment of cytomegalovirus disease and is active against variola virus in vitro, continue in two animal models.

Work has continued on the discovery and development of antiviral agents against variola virus. At Vector the lead compound continues to be NIOCH-14, an analogue of tecovirimat, but another unrelated compound has shown promising activity against orthopoxviruses. CDC researchers continue to look at agents that act at different stages of virus infection.

With regard to antiviral agents that are active against variola virus in vitro and in animal experiments, the Advisory Committee further received reports from two regulatory agencies, the US Food and Drug Administration and the European Medicines Agency, on progress towards completing the studies required for licensure for the treatment of smallpox in humans. The two regulatory agencies informed the Advisory Committee that protocols to test the effectiveness and safety of therapeutics in the field at the time of outbreaks must also be developed as a prerequisite for potential licensure of those agents.

New animal models, including outbred ICR mice and humanized mice, are being examined for their value in smallpox research. Regulatory authorities have engaged in discussions with researchers and pharmaceutical companies about the acceptability of these models and their results.

The Advisory Committee also received reports on the continued evaluation of third-generation vaccines, clinical trials to study them, and updates on LC16m8, including post-marketing surveillance, and Imvamune®/Imvanex®, which is being added to the Strategic National Stockpile in the USA.

The WHO Secretariat reported on the biosafety inspection visits carried out at the two smallpox repositories (Vector in December 2014 and CDC in May 2015) and the next planned round of inspections. A brief update was also provided on the smallpox vaccine stockpile held by WHO.

The Advisory Committee received a report from the Chair of the Independent Advisory Group on Public Health Implications of Synthetic Biology Technology related to Smallpox which concluded that the nature of the risk of re-emergence of smallpox has changed significantly and is evolving. The Advisory Committee responded to the issues raised in the report regarding the implications for variola virus research as follows:

- The Advisory Committee recognized the need for increased preparedness to deal with the potential consequences of the synthesis and possible re-emergence of variola virus and encouraged the expansion of expertise in the area of laboratory biosafety and biosecurity and diagnostics for this purpose. It also recommended increased capacity of staff trained to work with dangerous pathogens and to recognize smallpox cases.
- The Advisory Committee concluded that there was no need to increase the number of sites where research using live variola virus could be undertaken beyond the two existing authorized global repositories, based on their assessment of the risk versus benefit. However, it recommended that more laboratories around the world should develop capacity for smallpox diagnostics which did not need live variola virus. The Advisory Committee also recommended that point-of-care diagnostic tests for variola virus infection should developed; their use should be coordinated to assure accuracy of testing in low disease prevalence situations.
- Given the change in the risk of re-emergence of smallpox due to synthetic biology technology, the Advisory Committee reviewed its terms of reference and concluded that they were broad enough to include the area of synthetic biology technology if needed. There was general agreement that the areas of current research – focusing on translational outcomes for diagnostics, therapeutics and vaccines – remain important.
- However, the Advisory Committee agreed that additional members with appropriate expertise related to new technologies, such as synthetic biology, would be welcome. The Advisory Committee gave special attention in its review of the current research agenda to assess whether there are or will be additional needs for smallpox control measures in case of re-emergence of a synthesized and/or modified variola virus.
- Finally, as recommended by the Independent Advisory Group on the Public Health Implications of Synthetic Biology Technology Related to Smallpox, the Advisory Committee revised the *WHO recommendations concerning the distribution, handling and synthesis of*