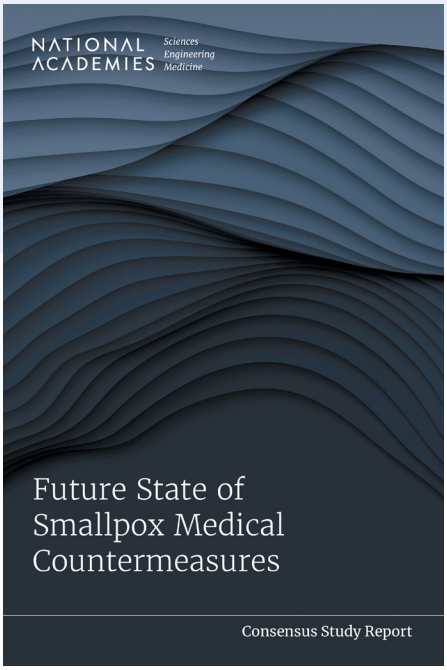
Future State of Smallpox Medical Countermeasures



THE CONTINUED CHALLENGE OF SMALLPOX

Smallpox is an ancient, devastating disease of humanity, taking the lives of 300–500 million people in the 20th century alone. After a decades-long global vaccination campaign, the World Health Assembly (WHA) declared smallpox eradicated in 1980 and no naturally occurring cases have occurred since. However, due to the potential for a deliberate, natural, or accidental reemergence, the United States has since worked to position itself against such an eventuality. These efforts have largely been focused on the development of smallpox medical countermeasures (MCMs), specifically diagnostics, vaccines, and treatments. This report, *Future State of Smallpox Medical Countermeasures*, examines U.S. readiness for smallpox amid shifting threats, lessons from outbreaks, and a changing landscape of technological innovation.

Real-world experiences with mpox (a related orthopoxvirus) and COVID-19 offer lessons that underscore the need for further domestic and global coordination for preparedness against smallpox, a disease caused by variola virus, and other members of the same viral genus, known as orthopoxviruses. These outbreaks have surfaced major challenges in scaling medical countermeasure development, manufacturing, distribution, and generating uptake. Finite budgets also necessitate difficult investment decisions for medical countermeasures in an era increasingly defined by emerging infectious disease.

Smallpox is unique among pathogens: although natural occurrence has been eradicated, by international agreement only two countries—the United States and the Russian Federation—possess remaining samples of live variola virus. Approved research to work with these samples facilitates better understanding of the virus and supports the development of improved diagnostics, vaccines, and treatments.

These research and development objectives necessitate the use of live virus; yet the fate of the approved viral collections is the subject of international debate. Furthermore, advancements in genome science and genetic engineering raise the possibility of deliberate recreation and misuse of variola virus, considered appealing to terrorists for its potential to create a more lethal and transmissible strain.

At the request of the Administration for Strategic Preparedness and Response, an ad hoc committee convened by the National Academies of Sciences, Engineering, and Medicine evaluated the current state of research, development, and stockpiling of smallpox MCMs to inform a path forward that would optimize smallpox readiness. The committee comprised experts across disciplines including pox virology, infectious disease medicine, risk assessment, synthetic biology, global health law, public health practice and ethics, and other areas. Based on this evaluation, the committee developed findings and conclusions that may serve to inform U.S. government investment decisions in smallpox MCM readiness and the official U.S. position on the disposition of the live viral collections at future WHA meetings.

WHERE TECHNOLOGICAL RISK MEETS OPPORTUNITY

Genome editing, amplification, and synthetic engineering continue to evolve apace, with further potential acceleration by major advances in artificial intelligence. This innovation can be exploited for nefarious purposes to create engineered viruses in an era when the virus has been eliminated from natural circulation. The malicious exploitation of such technologies to create novel bioterror agents could render an established MCM ineffective. However, harnessing these same technological advancements for good could lead to improved MCMs that are easier to distribute and administer, reduce side effects, and protect against a range of orthopoxviruses, both natural and engineered.

The U.S. government maintains a national stockpile containing three types of smallpox vaccines, two types of smallpox antivirals, and a non-vaccine biologic for vaccinia-related complications. Designated Laboratory Response Network laboratories can run Food and Drug Administration (FDA)-approved tests to detect smallpox virus in clinical samples and differentiate it from other orthopoxviruses. Far more options for detecting, preventing, and treating smallpox are available now than during the pre-eradication period, when the primary tool in use was a single type of vaccine. These breakthroughs in vaccine development, antiviral therapies, and diagnostic tools that have benefitted U.S. smallpox preparedness are the product of innovative, advanced science and technology. And still, the MCMs that have been stockpiled are imperfect: some vaccines and treatments may lead to serious side effects; some are cumbersome to administer; and no diagnostics are available at health care offices or other points of use.

PREPAREDNESS FOR ANY RESPONSE SCENARIO

Smallpox readiness means readiness for any kind of outbreak: natural, accidental, or deliberate. The effectiveness of smallpox MCMs has been established largely based on their use against eradicated strains of variola. While one would expect existing MCMs to be effective against a reemergence of known strains of smallpox, they may be diminished against strains deliberately engineered to evade the vaccines and antivirals available today. Furthermore, these contingencies could occur in a social dynamic in which vaccine hesitancy and public concerns about potential side effects are an issue.

These kinds of considerations necessitate routine risk assessments; a transition to a modernized stockpile consisting of safe, effective, and easy-to-use countermeasures; and operational response plans and clinical guidance that are updated to reflect factors that may influence response success. Because the nation has never faced a smallpox outbreak in the 21st century, planners will also need to consider how the diverse MCMs available today, and in the future, will work together in a response; logistical and clinical considerations are paramount.

IMPROVING SMALLPOX READINESS AND RESPONSE

A successful response to a smallpox emergence will hinge on many capabilities that cut across sectors, disciplines, and levels of government. The report acknowledges the broader MCMs enterprise while addressing in detail two areas of specific relevance to the committee's task: (1) smallpox MCMs readiness and (2) systems readiness.

Proposed Priorities for Medical Countermeasures Readiness

Smallpox Research Agenda

- Research and development roadmap for live variola virus research
- Pathways to support the validation, approval and licensure, and commercialization of MCMs for orthopoxviruses

Diagnostics and Surveillance

Expanded diagnostics and surveillance supported by:

- multiplex nucleic acid assays for new platforms
- forward-deployed point-of-care assays
- FDA-approved serologic assays

Vaccines

Safe and effective single-dose smallpox vaccines that:

- can immediately contain outbreaks
- afford long-term protection
- are adaptable and scalable to protect against novel strains

Therapeutics

Diverse smallpox therapeutics options such as:

- antivirals with novel mechanisms of action
- combination antiviral treatments
- non-vaccine biologics such as monoclonal antibodies and antibody cocktails

Emerging Technologies

Periodic risk/benefit analyses for smallpox MCM research and development that take advantage of emerging technologies

The smallpox MCM assets held by the United States and the plans designed to make use of them must be continually updated and forward-looking to account for changes in science and technological capability, populations at risk for disease and adverse events from MCMs, and geopolitical factors. The following priorities set forth in the report could contribute to society's ability to prepare for and respond to a smallpox event amid this shifting landscape.

CONCLUDING REMARKS

As articulated in the report, the committee envisions a responsive and flexible system to establish research priorities for smallpox diagnostics, vaccines, and treatments, together with judicious stockpiling, and strategic plans for rapid and equitable distribution of MCMs in the event of a smallpox or other orthopoxvirus outbreak. The smallpox MCMs portfolio is mature compared to that for other threats and the goals of a mature portfolio should themselves mature with time. The scientific and technological opportunity for innovative and improved smallpox diagnostics, vaccines, and treatments may support a transitional phase for the smallpox MCM portfolio. In a transitional phase, investments made to date would be sustained to ensure a ready stockpile, while collaborations with other nations and organizations are leveraged to build a diversified smallpox MCM stockpile and an agile, distributed MCM response network of the future.

Proposed Priorities for Systems Readiness

Operational Considerations

Periodic assessment of operational factors that might influence smallpox readiness and response, such as:

- supply chain and manufacturing base considerations
- social aspects of MCM deployment and uptake
- needed updates to clinical and public health guidance and strategies
- regulatory readiness

Strategic National Stockpile

- Transition plan for the smallpox MCM portfolio to ensure a ready stockpile through sustainment of investments to date
- International collaboration to build a diversified smallpox MCM stockpile and an on-demand, distributed response MCM network of the future

Global Cooperation

U.S. investment and support in MCM research, development, and deployment capacities and capabilities internationally

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Copies of the Consensus Study Report are available from the National Academies Press, (800) 624-6242 or https://nap.nationalacademies.org/catalog/27652.

To read the full report, visit http://www.nationalacademies.org/Smallpox-Study.

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