

Future State of Smallpox Medical Countermeasures

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Committee on the Current State of Research, Development, and Stockpiling of Smallpox Medical Countermeasures

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Presentation Agenda

- 1 Study Approach
- 2 Background and Context
- 3 MCM Readiness
- 4 Systems Readiness
- 5 Concluding Remarks

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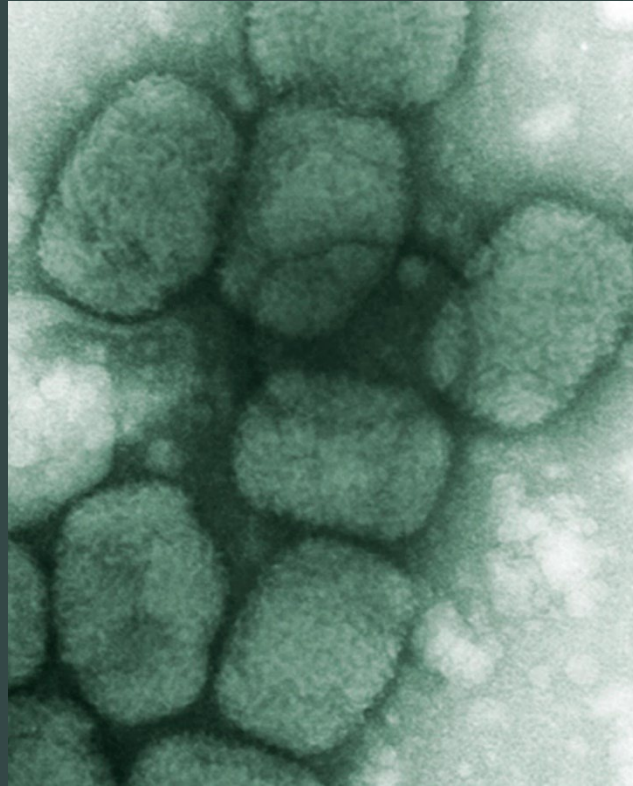
Study Approach

Statement of Task

Study Timeline

Study Scope

Structure of Report and Conclusions

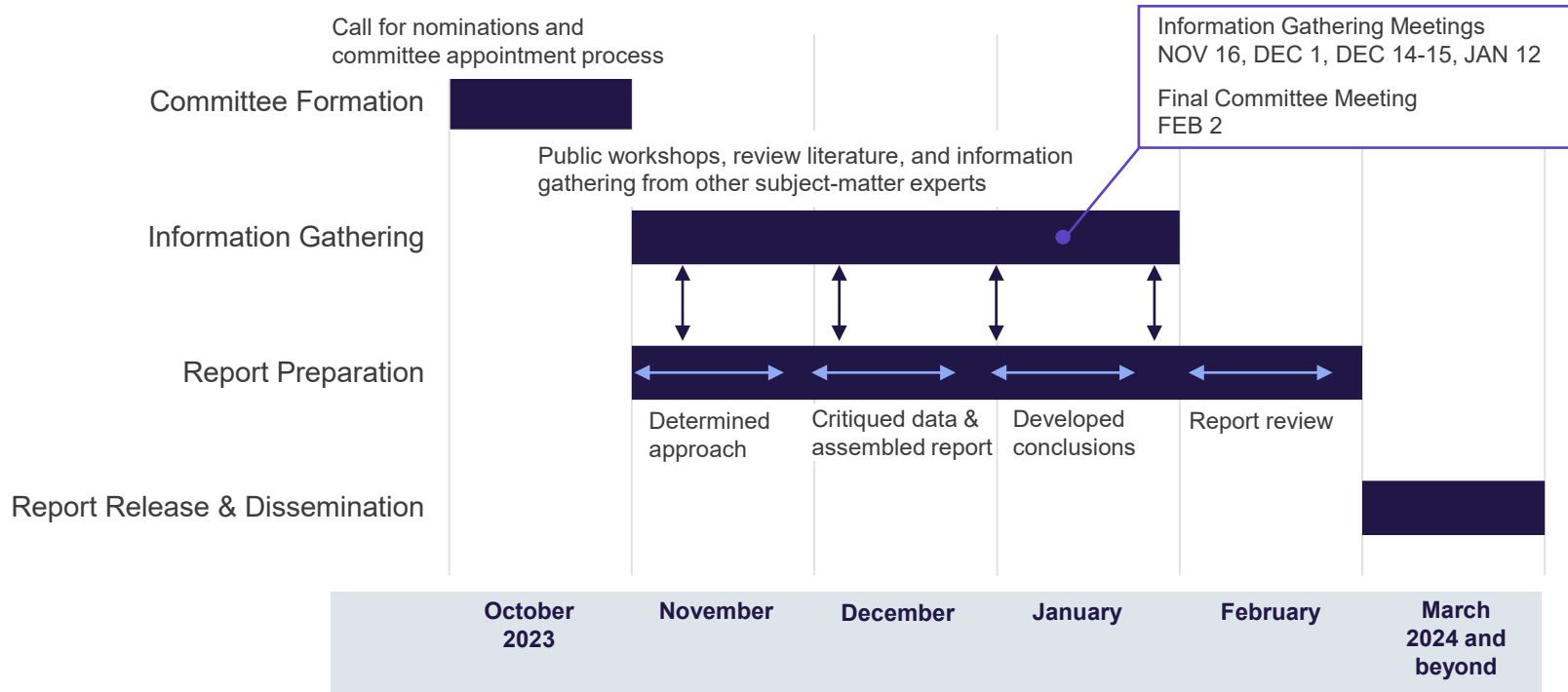


Statement of Task

1. Consider how the COVID-19 pandemic and the mpox multi-country outbreak can inform improvements to smallpox readiness and response, including the availability of smallpox MCMs and the ability to meet potential demand.
2. Examine the current state of MCMs for the diagnosis, prevention, and treatment of smallpox, including:
 - a. How the mpox outbreak altered assumptions about the efficacy and utility of smallpox MCMs.
 - b. The continued role of live variola virus for research and public health purposes.
 - c. Implications for the composition of smallpox MCMs in the U.S. Strategic National Stockpile (SNS)
3. Explore the benefits and risks of scientific and technological advances on smallpox readiness and response and identify key priorities in research and development of smallpox MCMs.

Building on the Institute of Medicine's previous reports, *Assessment of Future Scientific Needs for Live Variola Virus* (1999) and *Live Variola Virus: Considerations for Continuing Research* (2009), and a review of existing literature, analyses, and other expert and public input, the committee will develop a report with its findings and conclusions on priorities for additional research or activities to improve the U.S. government readiness and response posture against smallpox, and on the composition of the SNS to ensure appropriate smallpox MCM response options.

Study Approach and Timeline



Study Scope

Topics considered within scope:

- The utility of smallpox MCMs and implications for smallpox readiness and response considering lessons learned from recent public health emergencies.
- Strategic approaches for stockpiling smallpox MCMs and an enumeration of the ways in which research using live variola virus could provide benefits in a smallpox outbreak.
- Findings and conclusions on the statement of task (no recommendations).

Topics considered out of scope:

- Determinations about the destruction or retention of live variola virus collections.
- Challenges with developing vaccines and therapeutics for special populations (e.g., pediatric populations, pregnant and lactating persons, immunocompromised persons, etc.).
- Detailed threat or risk assessments (e.g., potential for a smallpox outbreak, risks of live variola virus research, risks of dual-use research of concern, etc.).

Structure of Report and Conclusions

Report Structure:

- **Chapter 1:** *Introduction*
- **Chapter 2:** *State of Smallpox MCM Readiness*
- **Chapter 3:** *Factors Influencing Smallpox Readiness*
- **Chapter 4:** *Way Forward: Priorities for Research, Development, and Stockpiling*

Conclusions:

- The committee formulated **7 overarching conclusions** across two key aspects of smallpox readiness and response: (1) medical countermeasures readiness, and (2) systems readiness.
- The committee also formulated **24 chapter-specific technical conclusions**.

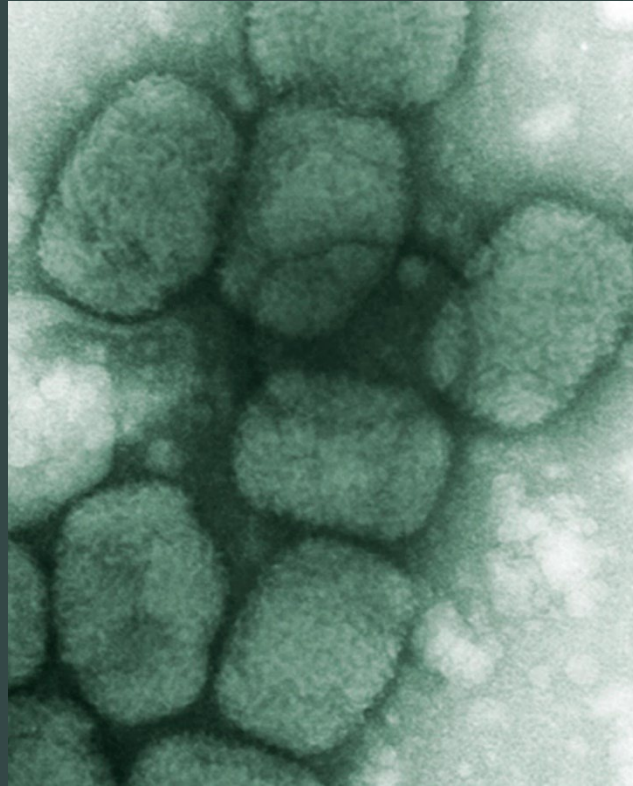
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Background and Context

Historical Context

Lessons Learned from COVID-19 and mpox

Smallpox Emergence and Response Factors



Smallpox Emergence and Response Considerations

The committee considered the following factors in their evaluation of MCM readiness:

- Environmental resurrection/mutation and engineered variola or variola-like virus
- Accidental and deliberate release of variola virus
- Geographic scope
- Immediate containment and long-term, post-event
- MCM development, storage, and administration (commercial manufacturing capability, future development and utility of MCMs, storage requirements, distribution requirements, vaccine administration)
- MCM utility and acceptance (changing population characteristics, vaccine and therapeutic safety and applicability, acceptance and willingness to use MCMs)

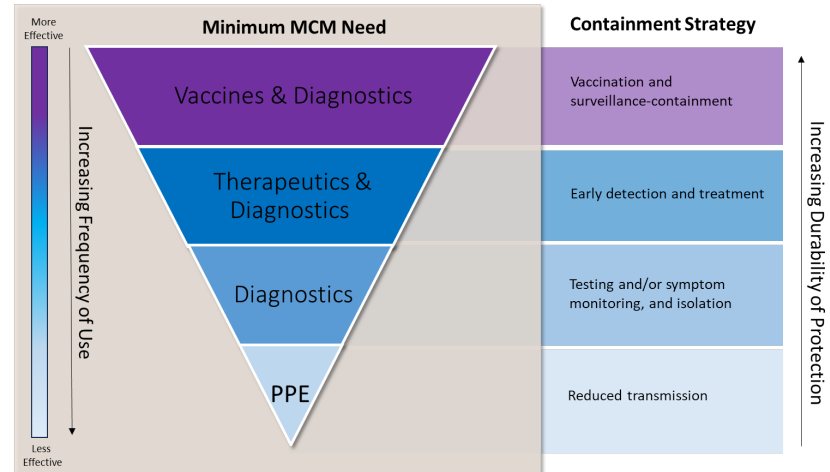


FIGURE 1-2 Minimum smallpox MCM needs according to containment strategy.

SOURCE: Adapted from Biggs and Littlejohn (2022).

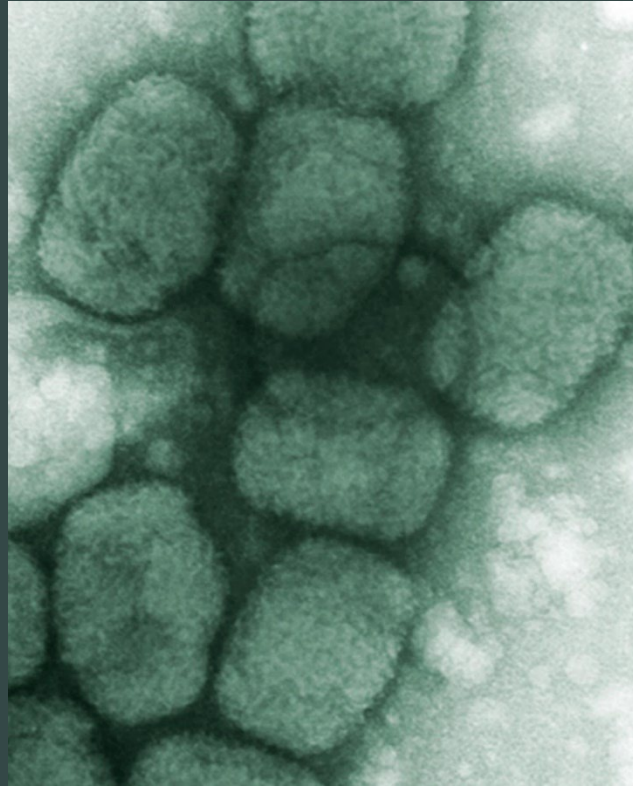
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MCM Readiness

Smallpox MCM Utility, Gaps, and Opportunities

Evolving Biothreat and Technology Landscape

Variola and Non-Variola Orthopoxvirus Research



Summary of Priorities - Medical Countermeasures Readiness

Smallpox Research Agenda

- R&D roadmap for live variola virus research.
- Pathways to support validation, approval & licensure, and commercialization of existing and next-generation MCMs for non-variola orthopoxviruses.

Ongoing Risk/Benefit Analysis

- For smallpox MCM research and development using emerging technologies.

Expanded Diagnostics and Surveillance

- Multiplex nucleic acid assays for new platforms, field settings, and use with clinical samples prior to rash illness.
- Forward-deployed point-of-care assays (e.g., protein- or antigen-based tests).
- FDA-approved serologic assays to assess individual and population levels of immunity against smallpox and history of exposures.

Safe and Efficacious Single-Dose Vaccines

- Utility for immediate outbreak containment & long-term protection.
- Quickly adapted and developed at scale if needed to protect against a novel strain.

Diverse, Safer, Therapeutics Options

- Antivirals with different and diverse targets, mechanisms of action, and routes of administration.
- Combination antiviral treatments and treatments based on novel technologies and platforms.
- Vaccinia immune globulin intravenous (VIGIV) repurposed as part of combination therapy.
- Options for biologics (e.g., monoclonal antibodies, antibody cocktails).

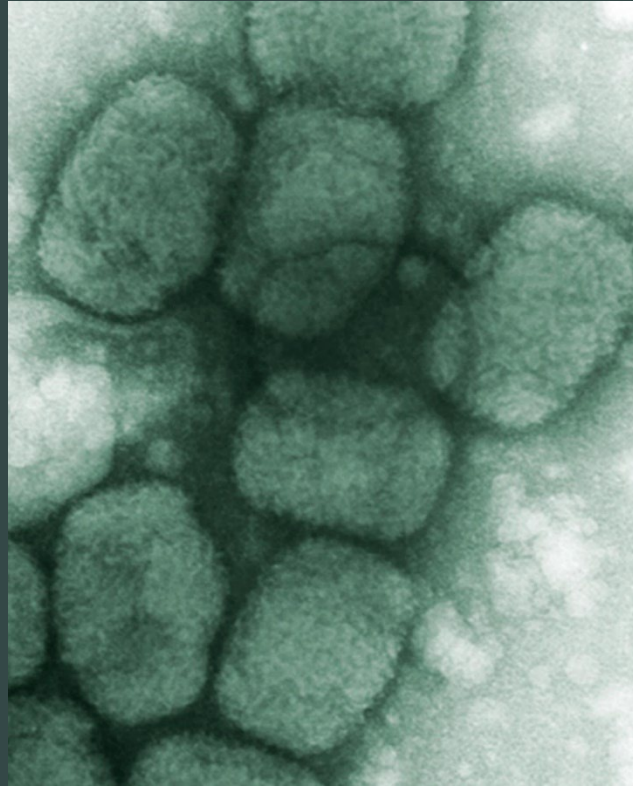
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Systems Readiness

Operational Considerations for Smallpox
Readiness and Response

The Strategic National Stockpile and the
Smallpox MCM Portfolio

Global Cooperation



Summary of Priorities – Systems Readiness

Operational Considerations

Periodic assessment of implementation and operational factors that might influence smallpox readiness and response including, manufacturing capacity, frontline readiness, risk communication, and regulatory readiness.

Strategic National Stockpile

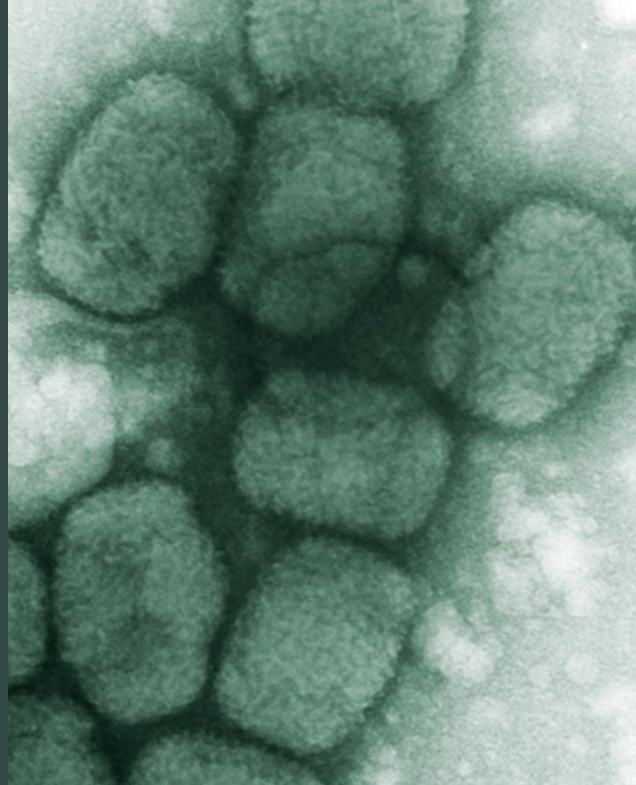
Transition plan for the smallpox MCM portfolio, in which investments made to date are sustained to ensure a ready stockpile—while working with other nations and organizations to build a diversified smallpox MCM stockpile and an agile, on-demand, distributed response MCM network of the future. Budgetary stress on stockpile purchases and maintenance could be reduced through the commercialization of these smallpox MCMs for non-variola orthopoxviruses.

Global Cooperation

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

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Concluding Remarks



Concluding Thoughts on Smallpox MCMs

Steady progress in past 20+ years in:

- Smallpox MCM **research and development**, and **regulatory review**.
- **Work with variola-related viruses** (orthopoxviruses- vaccinia, cowpox, mpox), and variola, is **critical for these achievements**, and will continue to be important and essential for improvements.
- Extended treatment with currently licensed drugs can **lead to development of antiviral resistance** - additional research and **development on treatments and treatment strategies**, and **rapidly protective prevention** is critical.
- Specific **considerations to protect a population with greater immune impairment** or dysregulation.
- Biosafety and biosecurity considerations per **restricted handling of live variola well addressed** and reviewed (international and national authorities).

Concluding Thoughts on Readiness

Readiness of the entire MCM enterprise, including:

- **Readiness for MCM availability** – options for manufacturing, stockpiling, commercialization, etc.
- **Global demand** for testing, treatment, and prevention MCMs during a smallpox emergency is anticipated - **regulatory readiness important** to make improved MCMs available.
- **Readiness to respond, particularly at the front lines.**
- **Tiered exercises to assess readiness and response** at all levels—federal, state, county, tribal, territorial—our readiness is likely the weakest at the point of getting MCM to those who need them, in a consistent and timely manner.

Concluding Thoughts on Diagnostics

Experiences with COVID-19 and mpox further informed thinking on:

- Benefits of **smallpox MCM work extends to other emerging orthopoxvirus illnesses** (mpox, vaccinia like viruses, cowpox, Alaskapox) - in turn, studies that inform **MCM use for these illnesses can be used to support smallpox MCM** development.
- Demand for **broader availability of diagnostics to be expected**, as evident through the experiences of COVID-19 and mpox.
- Beyond MCM research and development, frameworks to **accelerate implementation research investigating the operational and social aspects of deploying and uptake** of smallpox MCMs.

Concluding Thoughts on Emerging Biotechnologies

Accelerating pace of technological advancements in biology and artificial intelligence:

- **Presents benefits** to improve MCM effectiveness and access through distributed technologies.
- Will continue to present **policy and readiness challenges due to potential for nefarious use.**
- **In particular, DNA synthesis** might **contribute to risk.**
- **AI models could be used** to mitigate outbreak spread by understanding how variola virus might naturally evolve and could aid those seeking to render existing treatments ineffective.

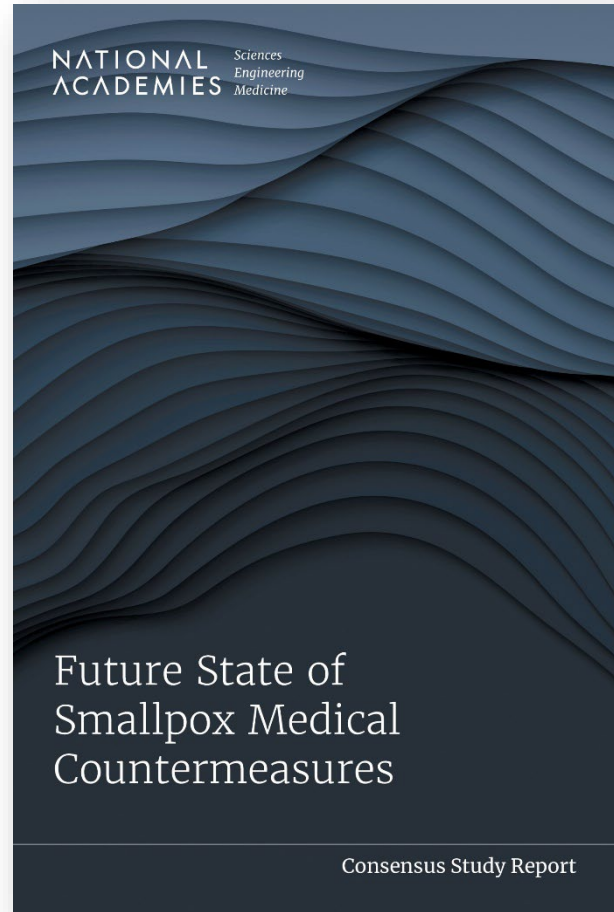
Summary of Report Vision and Main Messages

- **Vital to prioritize research into and the development of safer and more effective smallpox MCMs**, to make **judicious choices about stockpiling**, and to have modern, well rehearsed, and adaptable strategic plans in place to respond nationally and globally in the event of a variola or other orthopoxvirus outbreak.
- These efforts **will depend on rapid identification (diagnostics and surveillance), effective containment and response, equitable allocation, and global solidarity.**
- The **committee envisions a responsive and flexible system**, and this type of system **will require U.S. and international partners** to plan and respond in the face of multiple scientific, societal, political, and ecological uncertainties.
- These uncertainties—and **lessons learned from COVID and mpox—argue for research and stockpiling decisions to be made in anticipation of the next potential threat**, with a readiness to shift priorities rapidly in the face of emerging information.

Thank you!

Questions about the Study?

Contact Lisa Brown, Study Director, at LBrown@nas.edu



Historical Context

- Policy milestone
- Emergency event
- ◆ Technology milestone

■ **1980** Smallpox declared eradicated - WHA33.4 recommends post-eradication measures (e.g., limiting remaining viral specimens, establishment of physical international reserve of smallpox vaccines).a

■ **1986** WHO Ad Hoc Committee on Orthopoxvirus Infections recommend to destroy remaining viral specimens by Dec 31, 1993.

● **1977** Last naturally occurring smallpox case.

■ **1982 – 1983** Viral specimens consolidated to U.S. and Russian laboratories.

◆ **1994** Full genome of variola virus strain sequenced.

■ **1998-1999** IOM report on “Assessment of Future Scientific Needs for Live Variola Virus” report; U.S. establishes smallpox research program.

■ **1999** U.S. Congress directs CDC to establish U.S. national pharmaceutical and vaccine stockpile for biochemical threats.

WHA 52.10 authorizes retention of variola virus collections and to delay destruction until 2002; ACVVR established.

■ **1996** WHA 49.10 recommends remaining collections of variola virus to be destroyed on Jun 30, 1999.

■ **2002** WHA 55.15 authorizes retention of variola virus collections until research goals are achieved.

WHA 55.16 urges shared resources in an emergency. Virtual Smallpox Vaccine Emergency Stockpile (SVES) established.

● **2001** September 11th terrorist attacks in the U.S.

■ **2002** Stockpile renamed SNS, U.S. pledges 20 million doses of smallpox vaccine to virtual global stockpile.

● **2003** U.S. mpox outbreak.

■ **2005** International Health Regulations (IHR) updated following SARS pandemic.

■ **2007** WHA 60.1 recommends major review of variola virus research in 2010.

■ **2008-2009** IOM committee reviews unmet needs of research with variola virus; publishes “Live Variola Virus: Considerations for Continuing Research”.

■ **2011** WHA 64.11 reaffirms need to reach consensus on proposed new date for destruction of variola virus stocks.

● **2009-2010** H1N1 pandemic declared a public health emergency of international concern (PHEIC).

◆ **2013** CRISPR-Cas9 adapted for gene editing.

● **2015** Alaskapox virus emerges.

● **2017** Mpox reemerges in Nigeria after four decades.

◆ **2018** Horsepox virus synthesized de novo.

■ FDA approves tecovirimat for treatment of smallpox.

■ **2019** FDA approves MVA-BN for smallpox and mpox prevention.

■ **2021** FDA approves brincidofovir for treatment of smallpox.

Negotiations re-open for addition of anti-virals to SVES.

● **2020** COVID-19 pandemic.

● **2022** Mpox multi-country outbreak.

◆ OpenAI launches ChatGPT generative AI platform.

● **2023** DRC mpox clade 1 outbreak.

Lessons Learned From COVID-19 and Mpox

Diagnostic and Testing Availability and Access

- Delays in rolling out and scaling up laboratory-based testing capacity.
- Challenges in supply chains for testing materials.
- Lack of point-of-care testing early on.

Vaccine and Therapeutic Availability, Access, and Uptake

- Success in rapid development of vaccines but tempered by unanticipated levels of vaccine hesitancy and mis/dis-information. (COVID-19)
- Success in having an existing stockpiles of vaccines but challenged to provide vaccine at scale as the stockpiled quantity was based on different assumptions. (mpox)
- Role of effective therapeutics was essential—dynamic between vaccine and therapeutic acceptance.
- Lack of established framework for clinical trials.

Global Cooperation

- Need for rapid detection, containment, and coordinated response locally to mitigate impacts at national, regional, and global levels.
- Shortfalls of the global MCM enterprise to ensure equitable access to MCMs hindered disease containment.

Smallpox MCM Utility, Gaps, and Opportunities

Diagnostics, Detection, and Surveillance

- Concerns with clinical recognition capability, limited availability of diagnostic assays, and lack of FDA-cleared serological assays.
- Opportunities to develop point-of-care tests, expand PCR assays and platforms, and leverage advancements in genomic and environmental surveillance.

Vaccines

- Safety concerns with first and second-generation vaccines, utility of third-generation vaccines for immediate smallpox containment uncertain due to two-dose regimen.
- Limited vaccine production capacity drives dependence on SNS to maintain sufficient stockpile for entire U.S. population.
- Opportunities to develop safer, scalable vaccines based on multi-vaccine platforms and develop immunobridging strategies.

Therapeutics

- Initial approach based on small molecule compounds, more recently biologics focused.
- Concerns for antiviral resistance and adverse events with antiviral options, vaccinia immunoglobulin (VIGIV) not considered effective standalone therapeutic for smallpox.
- Opportunities to investigate utility of antivirals with distinct mechanism of action to existing options, antiviral combinations, antibody cocktails, and custom designed antivirals leveraging emerging technologies.

Technical Conclusions on Smallpox MCM Opportunities

(2-1) **Tests that can more accurately detect smallpox and other orthopoxviruses than those available today are needed**; efforts should focus on (1) adapting multiplex nucleic acid assays for new platforms and field settings, (2) developing forward-deployed (POC/PON) assays to enhance equitable access to tests, including protein or antigen-based tests to rapidly test and isolate infected patients, (3) identifying FDA-approved serologic assays to assess individual and population levels of immunity against smallpox and history of related exposures, (4) validating nucleic acid testing using a variety of clinical samples, (5) developing different categories of laboratory tests for different biosafety levels, and (6) supporting a global network of laboratories to detect, diagnose, and conduct surveillance in humans and the environment.

(2-2) **Smallpox vaccines that have improved safety across different population subgroups and are available as a single dose would support faster and more effective response** to contain smallpox and other orthopoxvirus outbreaks. The development of novel smallpox vaccines using multi-vaccine platforms (i.e., use common vaccine vectors, manufacturing ingredients, and processes) would improve the capacity for rapid vaccine production in response to a smallpox event and reduce the need for stockpiling in the SNS at current levels.

(2-3) To treat smallpox, the following would be advantageous to develop in order to supplement the therapeutic options currently approved and stockpiled in the SNS (1) **new, safer antivirals with different and diverse targets, mechanisms of action, and routes of administration** that minimize damage to host cells and have a high barrier to the development of resistance; (2) **combination antiviral treatments and treatments based on novel technologies** and platforms (e.g., genome editing, non-conventional targets, etc.); (3) **Vaccinia immune globulin intravenous (VIGIV) repurposed** as part of combination therapy; (4) diverse options for non-vaccine biologics including **monoclonal antibodies** and antibody cocktails.

Evolving Biothreat and Technology Landscape

Evolving Biothreat Landscape – Orthopoxvirus Outbreaks

- Changing threat landscape is evidenced by the increasing frequency and scope of orthopoxvirus outbreaks in recent years.
- Orthopoxvirus pathogenesis mechanisms are generally poorly understood.
- Identification of conserved targets or antigenic epitopes among different poxviruses could facilitate the development of broad-spectrum antivirals and vaccines.

Evolving Research and Technology Landscape

- Emerging biotechnologies promise rapid, reliable, and local production of MCMs.
- Modern risk-reduction strategies must account for additional risks posed by synthetic biology, gene editing, and gene sequencing.
- Convergence of AI, synthetic biology, and reverse genomics could eventually allow orthopoxviruses to be prototyped.
- Potential policy opportunities regarding sequencing and publishing additional poxvirus genome sequences. AI-based tools are limited by the number of available poxvirus genome sequences for training models.

2

In addition to smallpox readiness, research should continue to be used to enhance readiness and response for other orthopoxviruses, this includes **supporting the validation, approval and licensure, and commercialization of existing and next-generation MCMs for use in the management of non-variola orthopoxviruses** as an efficient way to expand readiness more broadly by enabling vendor-managed inventory approaches to stockpiling.

Technical Conclusions on Orthopoxvirus Research

(3-1) **The increasing recognition of orthopoxvirus illnesses in humans merits ongoing research and development of MCMs to detect, prevent, treat, and respond to these diseases.** This is of particular importance for mpox that is an ongoing global outbreak and is expected to be a long-term threat. Other emerging orthopoxviruses (e.g., Alskapox, cowpox, and vaccinia-like viruses) also need to be closely monitored as the population immunity against orthopoxviruses continues to wane.

(2-4) Most mpox therapeutics were developed because of investments in smallpox therapeutics, resulting in products found to have activity against mpox. **Direct investment in developing therapeutics targeting circulating orthopoxviruses could similarly benefit smallpox therapeutic preparedness** and could likely have more immediate utility and potentially achieve commercial viability.

3 A comprehensive and ongoing **risk–benefit analysis is needed for smallpox MCMs research** using emerging technologies as well as ongoing careful oversight to mitigate the risks of this research and ensure the risk–benefit balance is maintained.

Technical Conclusions on Emerging Technology

(3-4) The potential exists to synthesize the complete or partial variola virus genome and to manufacture infectious viral particles based on published genomes. Targeted modifications to the genome are also possible, which could alter functional components of the virus that could affect transmissibility or virulence. This capacity means that **even the guaranteed complete eradication of all existing smallpox collections today would not guarantee against its re-emergence as a threat.** It also introduces greater challenges in readiness planning by introducing the **possibility of atypical epidemiological or clinical presentations of the disease.**

(3-5) **Advances in emerging biotechnologies could also allow for the rapid development and deployment of MCMs.** A global, real-time, distributed, manufacturing network could enable safe and equitable production of smallpox diagnostics, vaccines, and therapeutics when and where needed to rapidly bring an outbreak anywhere in the world under control. A strategic research and development program promoting the development of general capability in this regard has the potential to unlock such a future.

Smallpox Research

The objectives of the U.S. smallpox research program derive largely from the 1999 IOM Report. Research objectives focus on enhancing the safety, efficacy, and utility of smallpox diagnostics, vaccines, and therapeutics.

Research with live variola virus and with non-variola orthopoxviruses is necessary to the development of smallpox MCMs.

Role of Non-Variola Orthopoxvirus Research

- Research of vaccinia virus, mpox sub-unit and nucleic acid vaccines (including mRNA vaccines), and modified Vaccinia Ankara (MVA) vaccine platform are rooted in the understanding of non-variola orthopoxviruses.

Role of Live Variola Virus Research

- IOM's 1999 finding that live virus is needed for certain aspects of research remains true today.
- Additional work in genomic sequencing of live variola virus will be required to advance the fundamental understanding of smallpox and related poxviruses.

Research Readiness

- Ability to evaluate safety and efficacy of MCMs against disease causing smallpox strains is critical.
- Research during emergencies often present unique challenges requiring tailored or adaptive study designs and infrastructure.

4

For the foreseeable future, **some research with live variola virus remains essential to achieving public health research goals** against an ever-evolving biothreat landscape and the potential for orthopoxviruses to emerge naturally or deliberately.

Technical Conclusions on Live Variola and Non-Variola Orthopoxvirus Research

(3-2) Variola virus-specific research is extremely restricted and is only undertaken when it is necessary and essential for public health. **It is not possible to fill knowledge gaps without the study of other orthopoxviruses.**

(3-3) **Gaps exist in the fundamental understanding of variola virus and non-variola orthopoxvirus** biology, pathogenesis, immunity and host-interactions, evolution, transmission, and ecology. Basic poxvirus research is beneficial to smallpox MCM development and contributes to readiness against other known and potential novel orthopoxviruses affecting humans. General advances in developing orthopoxviruses as vaccine vectors, gene delivery, and oncolytic virotherapy can have multiple benefits, including enhancing smallpox MCMs.

(4-1) **Research with live variola virus is essential** for developing animal models to be used for MCM efficacy testing as a human surrogate, full verification of the potential efficacy of MCMs, and the development of certain targets for more effective therapeutic options, and it may be essential if advanced organoid or other sophisticated systems will be used to study these biologic interventions.

(4-2) **Discovery research and pathogenesis research with live variola virus has merit as biomedical research** without an immediate obvious connection to smallpox readiness and response.

(4-3) It is important to **plan for clinical trials (e.g., of vaccine comparative effectiveness in conjunction with therapeutics and diagnostic testing) that will take place under real-world conditions during a smallpox outbreak** to ensure that the following are in place: adaptive and streamlined trial designs, efforts towards diverse and equitable patient participation, and regulatory protocols that have been pre-approved.

Operational Considerations for Readiness and Response

Manufacturing Capacity

- Reliance on a few smallpox MCM manufacturers
- Warm base lines, just-in-time manufacturing
- Commercialization of cross-protective orthopoxvirus MCMs

Access and Uptake

- Understanding dynamic between MCM access and acceptance to model uptake scenarios
- Continuous improvement informed by implementation research
- Vaccine hesitancy and risk communication

Frontline Readiness

- Timely education to meet response demands
- Sustaining suspicion for possibility of smallpox in patients with fever and rash
- Clinical guidance for smallpox MCMs and patient engagement to frontline providers
- Biosafety measures and special pathogen handling

Regulatory Readiness

- Timeliness and ability to expand
- Emergency use of investigational products
- Shelf-life extension
- Animal Rule
- Regulatory flexibility

5

Readiness and response efforts involving MCMs are complex due to many factors. MCM development, stockpiling, and distribution planning must be flexible, adaptable, and robust against multiple potential smallpox event scenarios. **Planning strategies should account for the complexities of each scenario** and aim to support several health and well-being outcomes (e.g., health, justice, equity, and national/international demand).

Technical Conclusions on Operational Considerations

(3-6) The small number of manufacturers of smallpox MCMs is a readiness and response vulnerability—and it is **clear there is insufficient capacity to scale MCM production in the event of a large-scale smallpox outbreak** especially one of international in scope

(3-7) Given the lack of commercially available orthopoxvirus diagnostics, vaccines, and therapeutics, **planning for logistics and supply chain management considerations is critical**. Efforts could give consideration to developing plans to increase the number of smallpox vaccine and therapeutics manufacturers as well as optimizing current manufacturing capacities should they be needed in the shorter term.

(3-8) **Communicating the risk and benefits of smallpox vaccination versus infection will be critically important**. But experience with COVID-19 and mpox demonstrated that effective risk communication has been a challenge, especially considering vaccine hesitancy and the politicization of vaccination, and misinformation and disinformation. These same challenges could occur in a smallpox outbreak.

(3-9) **Implementation research investigating the operational and social aspects** of deploying and uptake of smallpox MCMs is needed to assess operational parameters that could affect readiness and response.

(3-10) Those on the frontline—health care providers, public health practitioners and laboratorians, and first responders—need to have the capabilities and capacities to effectively and equitably diagnosis, prevent, and treat in the event of a smallpox outbreak. **Clinical and public health guidance should be updated to reflect new data and new MCMs** and should take into consideration the range of response strategies beyond post-exposure programs (i.e., ring vaccination).

Continued...

(3-11) **Regulatory readiness and responsiveness, applicable to all types of MCMs, will be critical** in the event of a smallpox outbreak. This is especially relevant considering the additional laboratory biosafety concerns for smallpox compared with other orthopoxviruses.

(3-12) **New regulatory models that can quickly evaluate MCMs that use novel platforms and newer methodologies need to be developed and implemented.** This could be achieved through the sharing of necessary product characteristics, detailed submission requirements, and setting accepted benchmarks and immune assays (in the case of vaccines) ahead of time, as well as planning for surge staffing to ensure timely review and real-time engagement for inquiries.

Stockpiling Considerations

International Sharing of Burden and Benefits

- Leveraging regional and global partnerships and funding could alleviate burden on U.S. Government to fund and stockpile smallpox and orthopoxvirus MCMs.

Assessment Considerations for Smallpox MCM Portfolio

- Articulating different goals and milestones depending on MCM portfolio maturity.
- Examining potential uses of and implications for currently stockpiled MCMs for other orthopoxvirus outbreaks
- Diversifying stockpiled smallpox MCMs
- Developing framework to guide decision making if new smallpox MCMs are developed
- Optimizing maintenance and sustainment of current smallpox MCM stockpile
- Re-evaluating assumptions
- Planning for loss of manufacturing capacity

Operationalization Considerations for Smallpox MCM Portfolio

- Reviewing the deployment-ready stockpile formulation.
- Updating response plans and training and exercise tools to reflect current and potential new smallpox MCMs
- Planning for implementation, coordination, and communication up front

MCM-Specific Stockpiling Considerations

- Understanding specific indications and requirements of each MCM

6

The smallpox MCM portfolio is a mature portfolio, and the **goals of a mature portfolio should differ** from a relatively new MCM portfolio. The scientific and technological opportunity for innovative and improved smallpox MCMs **supports a transitional phase for the smallpox MCM portfolio**, in which investments made to date are sustained to ensure a ready stockpile—while **leveraging collaborations and partnerships with other nations and organizations** to build a diversified smallpox MCM stockpile and an agile, on-demand, distributed MCM response network of the future.

Technical Conclusions on the Strategic National Stockpile

(4-4) The nation relies on the SNS to deploy MCMs in response to a smallpox event because, currently, most of the necessary MCMs are not commercially available. **Moving forward, leveraging collaborations and partnerships with other nations and organizations to develop next-generation smallpox and orthopoxvirus MCMs and expanding the use of the current ones could create a shared burden and enable a pathway toward international sharing of benefits.**

(4-5) To facilitate a successful response in the event of a smallpox outbreak, **the suite of smallpox MCMs (diagnostics, vaccines, and therapeutics) will be deployed and must work in concert with one another.** However, the smallpox MCM suite has not been tested or exercised in this way: these MCMs were not used during the smallpox eradication campaign, some have not been deployed simultaneously before, and some are based on older technology and use outdated assumptions, including changes in population (e.g., demographic, physiological, and behavioral/risk perception).

(4-6) **Threat assessments and specific response scenarios, based on different potential smallpox or orthopoxvirus events, are needed to assess and determine the necessary quantities and types of MCMs needed for various effective and equitable response strategies** (e.g., early detection, immediate versus long-term response, isolation of patients, quarantine of contacts, use of therapeutics for prophylaxis and treatment including pre-exposure prophylaxis with therapeutics for first responders and health care providers, ring vaccination, or mass vaccination).

Global Cooperation and Stockpiling

- Global preparedness and international cooperation critical for equitable and effective responses to emerging infectious diseases.
- Smallpox Vaccine Emergency Stockpile (SVES) established post-eradication – pledge stockpile consists of 31.01 million smallpox vaccine doses, U.S. smallpox vaccine pledge for 20 million people.
- Access to SVES vaccines coordinated through WHO and national regulatory authorities.
- COVID-19 and mpox multi-country outbreak demonstrated the speed which biothreats occurring internationally can affect and overwhelm national medical and public health response systems - highlighted shortfalls of global MCM enterprise in ensuring equitable access to MCMs both within U.S. and globally.
- Enduring concerns about public acceptability of countermeasures, presented a challenge in containing disease transmission around the globe.

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In a smallpox event, the U.S. readiness and response posture will be significantly affected by the ability of other countries around the world to adequately detect smallpox and contain transmission. Given global interdependence and global supply chains, **supporting MCM capacities and capabilities internationally (i.e., a global MCM platform) will improve security** against biothreats in the United States.

Technical Conclusions on Global Cooperation and Stockpiling

(1-1) The ability for many countries to contain a smallpox outbreak is currently dependent on the U.S. readiness and response posture to rapidly deploy MCMs upon request and in collaboration with WHO and global partners. Thus, **U.S. stockpiling decisions must take international commitments and equity arrangements into account.**

(1-2) The **U.S. pledge of smallpox vaccines to the WHO Smallpox Vaccine Emergency Stockpile (SVES) represents a substantial proportion** of what has been promised by WHO Member States. However, the number of doses in the SVES would likely be inadequate for a global response and would require additional MCMs to be produced to meet the demands of a response to deliver equitable access globally.