

# BOX THE POX

REDUCING THE RISK OF SMALLPOX  
AND OTHER ORTHOPOXVIRUSES

A PLAN BY THE  
BIPARTISAN COMMISSION ON BIODEFENSE

*February 2024*



**BIPARTISAN  
COMMISSION  
ON BIODEFENSE**

SPOTLIGHT

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# BACKGROUND

- Smallpox is highly contagious. It has an average incubation period of 10-14 days, and people can remain contagious for up to 20 days after symptoms begin.
- Initial symptoms include high fever, aches, and nausea. After several days of flu-like symptoms, patients will develop a rash that spreads to all parts of the body within 24 hours.
- The world eradicated smallpox in 1980. Routine smallpox vaccination among the American public stopped in 1972 after the United States eradicated the disease within its borders.
- While some in the United States are old enough to have been immunized against smallpox as children, their immunity has likely waned.
- Some military and other personnel more recently received smallpox vaccination, but relative to the population of the United States, that number is small.
- Prior to the monkeypox (Mpox) outbreaks in 2022, the Strategic National Stockpile (SNS) contained enough smallpox vaccine to vaccinate every person in the United States if an outbreak were to occur here.
- The SNS still contains smallpox vaccines and new stores currently exist in the public domain.
- Historically, smallpox vaccine prevented smallpox infection in 95% of those vaccinated but was less safe than other vaccines used today. Most people experienced normal, typically mild reactions to the vaccine, but approximately 1 in 1000 people had serious but not life-threatening reactions that required medical attention. During smallpox eradication in the 1960s, serious adverse events included death in one per one million vaccinations.
- Variola virus produces smallpox. Smallpox vaccine is made from live vaccinia virus, an orthopoxvirus similar to, but less harmful than, variola virus.
- One possible complication from the smallpox vaccine occurs when the vaccinia virus is spread by touching the vaccination site before it has healed or by touching bandages or clothing that have been in contact with the live virus from the vaccination site. This could further spread disease and confuse diagnosis.
- A biological attack using smallpox could occur in several ways (e.g., release of aerosolized particles, intentional infection of a terrorist who travels and spreads the disease). After initial infections, the virus would likely spread through secondary droplets (created by coughing or sneezing) and contact with the live virus on contaminated surfaces, including human cadavers.
- Up to 95% of the Native American population died from smallpox after the arrival of Europeans, who brought the disease with them.
- The Former Soviet Union (FSU) and other countries previously weaponized smallpox.
- The FSU did not provide evidence that it destroyed all of its stores of weaponized smallpox, having previously buried tons on Vozrozhdeniye Island, Uzbekistan.
- Orthopoxviruses (other than smallpox) continue to circulate and are the subject of ongoing research activities. Examples include Alaskapox, Camelpox, Cowpox, Horsepox, Monkeypox (Mpox), Mouspox, Raccoonpox, Skunkpox, Taterapox, and Volepox. Some are endemic in countries around the world and circulate in animals. Do not confuse with other genera (i.e., Parapoxvirus, Molluscipoxvirus, Yatapoxvirus, Capripoxvirus, Suipoxviruses, Leporipoxviruses, Avipoxvirus).



# INTRODUCTION

## **Smallpox and other orthopoxviruses pose significant threats to the United States and the world due to their potential for weaponization, accidental release, and vulnerability of populations who stopped routinely vaccinating against smallpox in the 1970s.<sup>1</sup>**

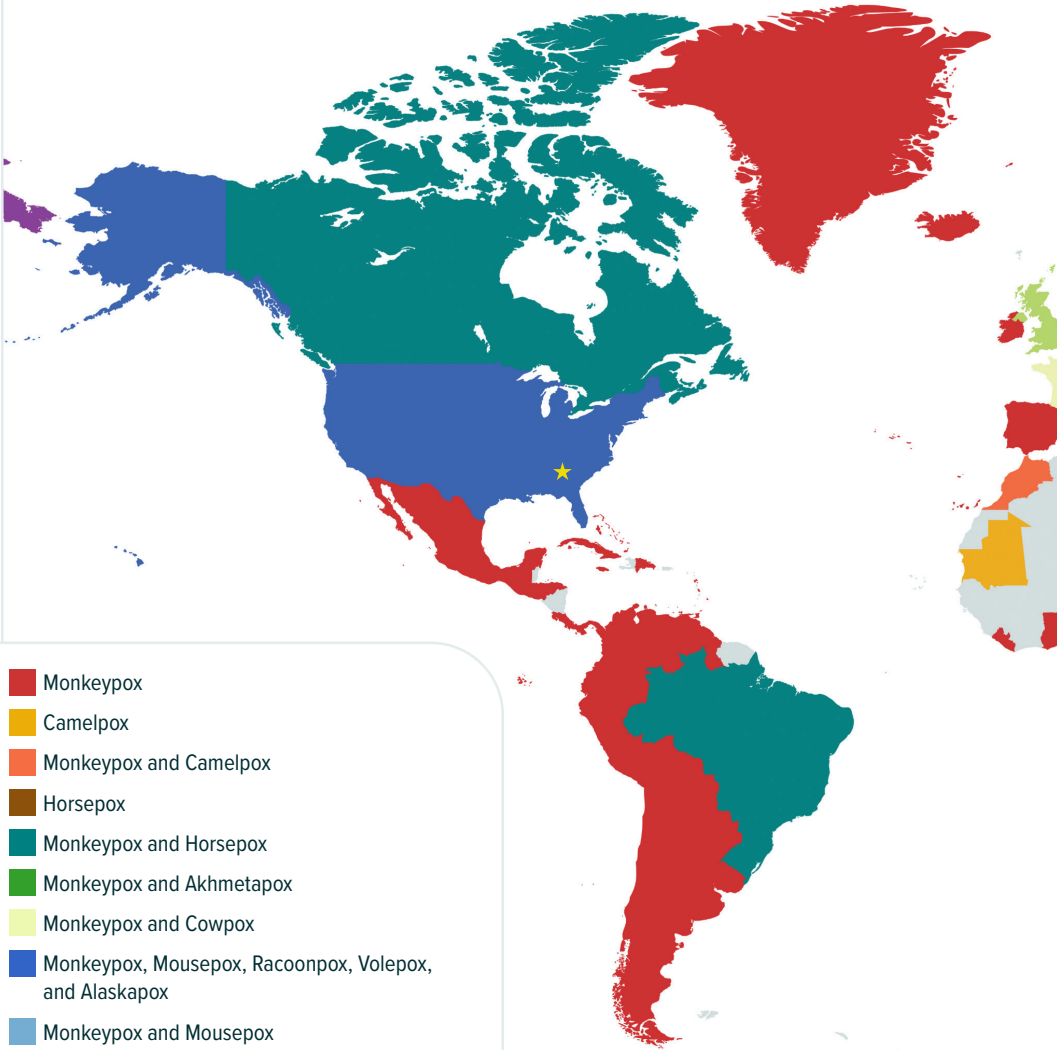
The FSU heavily researched smallpox as part of its bioweapons program and selected a notably potent strain, India 67 or India 1, to weaponize.<sup>2</sup> The FSU developed highly effective methods for large-scale production of this biological agent and maintained a yearly reserve of several hundred tons.<sup>3</sup> They engineered aerial delivery mechanisms, enhanced its virulence, and attempted to combine it with other viruses. The FSU also extensively researched Mpox and used it as a model to weaponize smallpox,<sup>4</sup> proving that bad actors could realistically use Mpox as a biological weapon.<sup>5</sup> Russia has not provided adequate proof that they destroyed their stockpiles of biological weapons and weaponized biological agents. In any case, they could produce and weaponize more smallpox now because they possess an active offensive biological weapons program,<sup>6</sup> applicable knowledge, and the virus.

The advancement of synthetic biology in recent years now means that others could weaponize smallpox. For example, Canadian researchers used mail-order DNA services in 2017 to synthesize the horsepox virus.<sup>7</sup> It took a small team with a little specialized knowledge, six months, and about \$100,000 to recreate the virus. Nation states, terrorist groups, or individuals could similarly recreate smallpox with relative ease at low cost.

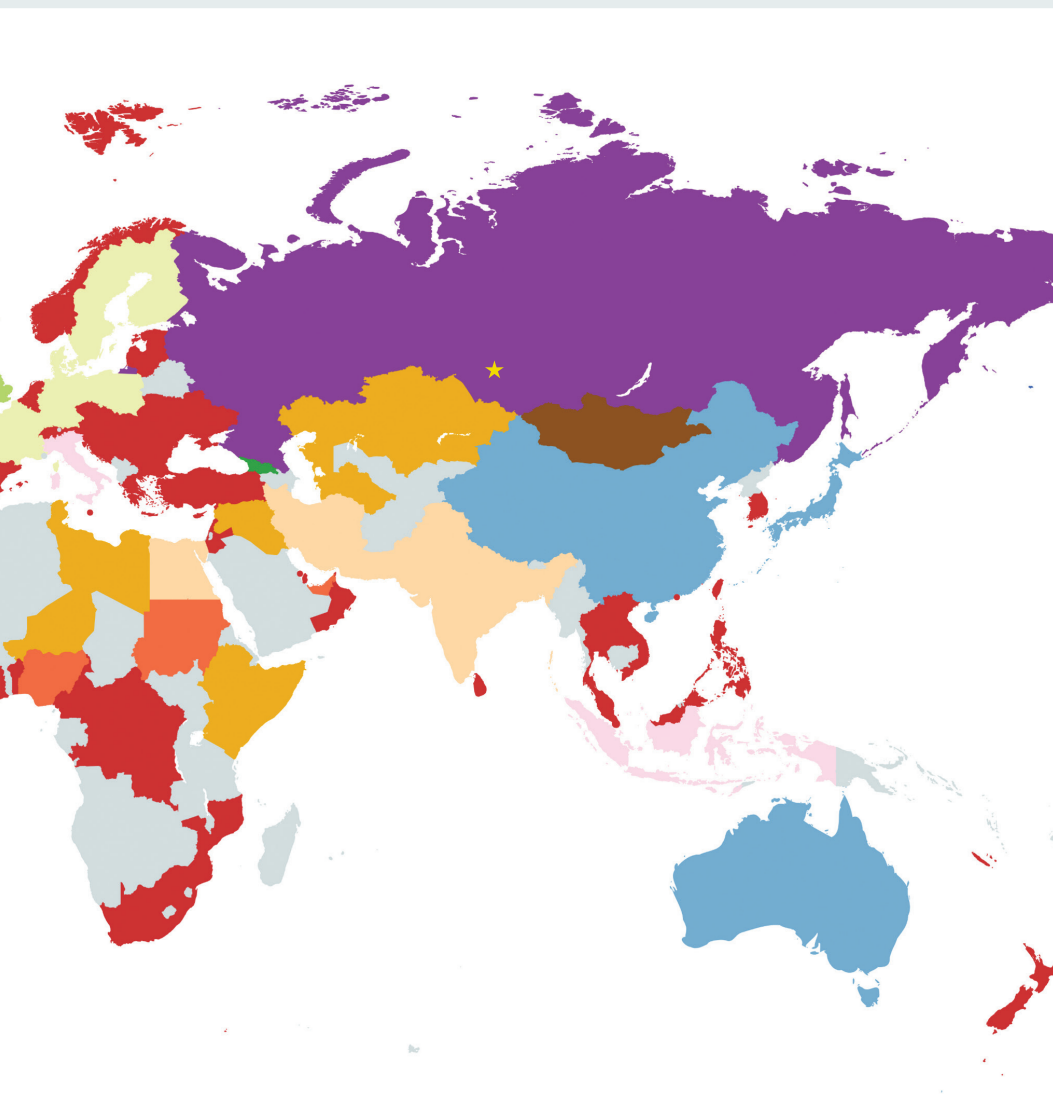
Deliberate attacks are not the only threat. The United States and Russia are the two countries known to possess smallpox virus samples. An accidental release from one of these repositories remains possible, although unlikely. Clandestine samples may exist elsewhere and if so, their security status is unknown. Accidental releases of other orthopoxviruses could occur in the 78 countries working with them.<sup>8</sup> Many orthopoxviruses still affect humans and animals (see Figure 1) and can lead to devastating outbreaks, epidemics, and pandemics.<sup>9</sup>

Orthopoxvirus threats, vulnerabilities, and consequences—especially from smallpox—could result in mass deaths, terrible economic hardship, and social unrest. We cannot afford to allow the reemergence of a disease that was once the scourge of humanity or for the emergence of other deadly orthopoxviruses while we are unprepared. The threat, our vulnerabilities, and the consequences of a disease with at least a 30% mortality rate place our country at much higher risk than that from other biological agents, a risk too great to ignore.

**Figure 1. Geographic Presence\* of Reported Orthopoxviruses<sup>10</sup>**



- Monkeypox
- Camelpox
- Monkeypox and Camelpox
- Horsepox
- Monkeypox and Horsepox
- Monkeypox and Akhmetapox
- Monkeypox and Cowpox
- Monkeypox, Mousepox, Raccoonpox, Volepox, and Alaskapox
- Monkeypox and Mousepox
- Monkeypox, Camelpox, and Buffalopox
- Monkeypox, Cowpox, Mousepox, and Buffalopox
- Monkeypox and Buffalopox
- Monkeypox, Cowpox, and Mousepox
- No reports
- Smallpox repository



*\*Historic reports of smallpox not shown on this map. Only locations of Variola virus repositories in Russia and the United States indicated. Lack of reporting in some countries may be due to lack of adequate biosurveillance infrastructure.*

# RECOMMENDATIONS

## PRODUCE BIOLOGICAL INTELLIGENCE

The Intelligence Community (IC) produces and consumes classified, unclassified, limited official use, and sensitive information on foreign activities. The IC bears the responsibility for collecting information, analyzing it, producing intelligence, and disseminating intelligence products regarding offensive biological weapons and those countries that maintain clandestine smallpox samples that could be used deliberately as a weapon.<sup>11</sup> Since the United States ceased its own biological weapons program in 1973, the government reduced its emphasis on the biological weapons threat. However, the IC never completely dropped the concern altogether and currently, 16 member agencies of the IC possess, or conduct activities in support of, biological intelligence programs.<sup>12</sup>

The IC must reinvigorate the intelligence cycle to collect, analyze, produce, and disseminate additional current biological intelligence. Key policymakers must make their needs known and provide requirements to the IC to drive the process. Not all intelligence needs will be about dual-use and other scientific endeavors that seem outside of IC purview.

In accordance with Recommendation 6 of the 2015 *National Blueprint for Biodefense*, the Commission recommends the following:

### **RECOMMENDATION 1: Strengthen capabilities to collect, analyze, produce, and disseminate biological intelligence about weaponized smallpox and other orthopoxviruses.**

Congress should amend the Intelligence Authorization Act to direct the Director of the Central Intelligence Agency, in coordination with the Under Secretary of Defense for Intelligence, to reinvigorate efforts to (1) determine the status of previously weaponized smallpox produced by the FSU;<sup>13</sup> (2) identify activities occurring in foreign laboratories that previously or currently work on biological weapons or in support of biological weapons research and development; (3) identify laboratories and other facilities that are part of offensive biological weapons programs in Russia and other countries where weaponized smallpox, clandestine samples, and other orthopoxviruses may be present (in violation of international norms and requirements) or to which these may have been transferred; (4) ascertain changes in foreign military doctrine about the use of biological weapons containing smallpox in combat; (5) investigate why countries such as North Korea continue to vaccinate against smallpox and possibly other orthopoxviruses;<sup>14</sup> (6) develop human sources of information in biological weapons laboratories and related facilities in Russia, North Korea, and other countries suspected to have offensive biological weapons programs that work, or are suspected of working, with weaponized smallpox and other orthopoxviruses; and (7) reach conclusions about intent to use biological weapons containing smallpox or other orthopoxviruses, and in what settings or situations.

## GET READY TO FIGHT AND WIN IN BIOLOGICALLY CONTAMINATED AREAS

The Department of Defense (DOD) must maintain a high level of combat readiness to fight and win in all battlefield scenarios, including those involving the use of biological weapons containing smallpox or other orthopoxviruses. The military achieves this readiness with rigorous training, advanced personal and other types of protective equipment, and with targeted vaccination programs. The Department requires smallpox vaccinations for military personnel and contractors performing duties or services that support its Chemical, Biological, Radiological, and Nuclear Response Enterprise.<sup>15</sup>

DOD also places great emphasis on public health, health promotion and education, preventative therapies, and medical countermeasures (MCM). The Department equips warfighters with detection and decontamination systems to minimize exposure and limit the impact of biological attacks when they are deployed to at risk areas.<sup>16</sup> The use of such weapons would present a significant challenge, however, and require swift medical response and robust coordination with local health agencies to prevent widespread infection and ensure the safety of military personnel, their families, and civilians.

In accordance with Recommendation 26 of the 2015 *National Blueprint for Biodefense*, the Commission recommends the following:

### **RECOMMENDATION 2: Strengthen the ability of the U.S. military to operate in environments contaminated with weaponized smallpox and orthopoxviruses.**

Congress should amend the National Defense Authorization Act to direct the Secretary of Defense to (1) enhance and update vaccination programs, strategies, and uptake; (2) research, develop, prototype, acquire, procure, and deploy less reactogenic<sup>17</sup> needle-free, transdermal, or minimally invasive vaccine and drug delivery technologies for rapid use for pre-deployment preparation and in combat environments; (3) expand health promotion and education programs to ensure that all military personnel are aware of the risks associated with biological weapons and the measures they must take to protect themselves; (4) research, develop, prototype, acquire, procure, and deploy next generation personal protective equipment (PPE), and decontamination methods for warfighter protection against weaponized smallpox and other orthopoxviruses; and (5) work with foreign militaries and foreign military organizations like the North Atlantic Treaty Organization (NATO) to conduct joint training exercises, coordinate information sharing, develop response plans for biological attacks involving weaponized smallpox and other orthopoxviruses, and share certain MCM in limited emergency situations.

## EVALUATE MEDICAL COUNTERMEASURE STOCKPILE NEEDS

People exposed to smallpox must be vaccinated within 3-7 days to prevent disease and death.<sup>18</sup> This is why we kept millions of doses of the vaccine in the SNS. There would not be time to hurriedly produce and distribute vaccine during a biological event involving smallpox. Stockpiled smallpox vaccines proved valuable in managing the 2022 Mpox outbreaks in the United States and would prove valuable in increasing protection for immunocompromised individuals, including pregnant women. Stockpiling decisions for smallpox (prior to the Mpox pandemic), however, did not historically factor in the possibility of using these MCM for threats other than smallpox. Additionally, it is unclear who is responsible for coordinating logistics (including the number of vaccination sites, mobilization of required personnel, and implementation of biosafety protocols for waste disposal) that would clearly impact MCM needs.

Although shifting some smallpox MCM to the commercial market helped, current supplies in the Stockpile do not yet meet requirements for preparedness set by the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). The same is true for other countries.

The shift of Mpox in Africa to the more lethal and sexually transmitted Clade I dictates that further clade shifts could create a more serious global health challenge even without nefarious actions by state/non-state actors). This, in turn, would create further potential risk of depletion of the SNS if the United States deployed vaccine globally. Though 42 USC 247d-6b(a)(2) requires annual threat-based reviews of the contents of the SNS, the statute does not currently require this review to consider the threat of all orthopoxviruses that smallpox vaccines, antivirals, and therapeutics could treat.

In accordance with Recommendation 22 of the 2015 *National Blueprint for Biodefense*, the Commission recommends the following:

### **RECOMMENDATION 3: Require periodic evaluation of smallpox medical countermeasure stockpile needs in consideration of the threat.**

The Secretary of Health and Human Services, in consultation with the Secretary of Agriculture, Secretary of Defense, and Secretary of the Interior, should include an assessment of orthopoxvirus diseases that could be mitigated by vaccines, antivirals, and therapeutics as part of the annual threat-based review of the SNS required by 42 USC 247d-6b(a)(2). Such examination should also consider smallpox vaccine, antiviral, and therapeutic needs for the Stockpile considering the previous, current, and potential use of these MCM to mitigate the impact of diseases caused by other orthopoxviruses.

## CONTINUE DIVERSIFICATION OF STOCKPILED MEDICAL COUNTERMEASURES

Determining the contents of the SNS is no easy task. The Secretary of Health and Human Services is responsible for making this determination, although the Secretary previously delegated that responsibility to the Centers for Disease Control and Prevention (CDC) and later, to the Department of Health and Human Services (HHS) Assistant Secretary for Preparedness and Response. The SNS contains or should contain antibiotics, vaccines, antivirals, other biological products, medical devices, and essential medical supplies. The Secretary of Agriculture is similarly responsible for the National Veterinary Stockpile.

During the 2022 outbreaks of Mpox that occurred throughout the world, the White House released smallpox vaccines and antiviral medications upon request by states, localities, and territories from the SNS to manage the spread of the disease,<sup>19</sup> and made vaccines commercially available. Today, contents of the Stockpile to address smallpox, Mpox, and possibly other orthopoxvirus diseases are diversified, although debate continues as to whether the contents are sufficient to meet PHEMCE requirements and national needs.

The US government would deploy all MCM determined to be at all effective—especially if the Food and Drug Administration (FDA) had already approved them for use to respond to smallpox—to try and control the spread of orthopoxvirus disease throughout our country. It made sense to only replenish the SNS with safer vaccine when Mpox spread to the United States. We must continue to diversify the smallpox MCM of the SNS with approved vaccines and antivirals we have at hand to (1) minimize the risk of supply chain disruptions; (2) maximize the ability to treat diverse populations and those with unique medical requirements; and (3) simultaneously invest in research, development, acquisition, and procurement of new smallpox MCM to reduce the risk associated with biological weapons containing smallpox.

In accordance with Recommendation 28 of the 2015 *National Blueprint for Biodefense*, the Commission recommends the following:

### **RECOMMENDATION 4: Diversify the contents of the Strategic National Stockpile with currently available, FDA-approved, smallpox vaccines and antivirals.**

Congress should amend the Pandemic and All-Hazards Preparedness Act (P.L.109-417) to direct the Secretary of Health and Human Services, in consultation with the Secretary of Defense, to continue to replace contents of the SNS when deployed throughout the Nation in response to orthopoxvirus outbreaks with a mixture of currently available, FDA-approved smallpox vaccines and antivirals. The Secretary of Health and Human Services should do so, recognizing the differing levels of safety, effectiveness, and efficacy of these MCM, and manage deployments of these contents accordingly. Congress should also provide sufficient resources to purchase vaccines, antivirals, and other therapeutics with regard to smallpox, understanding that these MCM could be used for other diseases caused by orthopoxviruses, as clearly demonstrated by Mpox.

## DEVELOP AND OBTAIN BROAD-SPECTRUM ANTIVIRALS

At the very beginning of an outbreak caused by a novel pathogen, those drugs already approved by the FDA, or those in clinical trials that can be rapidly deployed, will be our best pharmaceutical line of defense. We need to make investments in the development of antivirals that we can use to treat multiple viruses. Previous efforts to develop multi-pathogen therapeutics largely targeted direct-acting small molecule antivirals,<sup>20,21</sup> but targeting regions conserved across multiple viral species would also benefit from additional attention and investment. Having multi-pathogen therapeutics already in hand would help treat patients as early as possible in an outbreak.

The traditional approach of developing an individual MCM for each virus after it emerges leaves us insufficiently prepared. Multi-pathogen antiviral therapeutics would address a broad spectrum of viruses, much like broad-spectrum antibiotics address multiple bacteria. The National Institute for Allergy and Infectious Diseases<sup>22</sup> and the Defense Advanced Research Projects Agency<sup>23</sup> have made small investments in research on broad-spectrum antiviral therapeutics, but they and the Biomedical Advanced Research Development Authority (BARDA) need to invest more. In order to participate effectively in this development as well, the private sector needs advance market commitments and other government incentives to prevent market failures.

In accordance with the 2022 *Athena Agenda: Advancing The Apollo Program for Biodefense* recommendation to develop therapeutic drugs in advance of outbreaks, the Commission recommends the following:

### **RECOMMENDATION 5: Develop a suite of broad-spectrum antiviral drugs for orthopoxviruses.**

The Secretary of Health and Human Services, in coordination with the Secretary of Agriculture and Secretary of Defense, and in consultation with the Secretary of the Interior, should (1) develop novel broad-spectrum antiviral therapeutics for orthopoxviruses; (2) establish sustainable public-private partnerships with industry and academia for this research and development; (3) advance antiviral development for endemic orthopoxviruses through Phase 2 and 3 clinical trials to serve affected populations better; (4) advance antiviral development for orthopoxviruses that are not endemic through Phase 1 clinical trials to demonstrate safety; and (5) inform Congress of these efforts.



## DEVELOP AND OBTAIN POINT-OF-USE DIAGNOSTICS

Rapid testing that produces valid and reliable results will enable earlier detection. Tests that take more than three days to produce a result are essentially useless if a disease like smallpox were to occur in any area, because the disease would spread faster than these tests would produce results. Readily available, accurate, minimally-invasive, portable, and user-friendly rapid tests would obviate the need to conduct testing only in centralized laboratories, require individuals to present themselves in person for specimen collection, and quarantine people until they get results.<sup>24</sup> These rapid tests would also help the public health community collect larger amounts of data on populations affected by diseases and extend testing to those that cannot readily access laboratories or healthcare establishments.

The development, approval, manufacture, and distribution of new point-of-use diagnostic tests during pandemics challenge the United States. Our reliance on centralized laboratory diagnostics impedes quick response while people wait for days and weeks for results. Given the Nation's failures in the early stages of the COVID-19 pandemic, a similar void in technical competency and failure to reach out to industry in a timely fashion for scale-up of diagnostics would be disastrous. Although point-of-use diagnostics seem ideal, their use and interpretation can confuse the public, preventing effective screening for disease and biosurveillance, necessitating clear guidance and public education efforts.

In accordance with Recommendation 30 of the *National Blueprint for Biodefense*, the Commission recommends the following:

### **RECOMMENDATION 6: Rapidly develop, approve, scale, acquire, procure, and distribute point-of-use diagnostic tests for smallpox and other orthopoxviruses.**

The Secretary of Health and Human Services, in coordination with the Secretary of Agriculture and Secretary of Defense, and in consultation with the Secretary of the Interior, should rapidly approve, develop, scale, acquire, procure, and deploy point-of-use diagnostic tests throughout the Nation before a biological event involving smallpox or other orthopoxviruses occurs. The Secretary should (1) require the development of rapid point-of-use and laboratory diagnostics simultaneously; (2) develop and scale diagnostic capabilities quickly; (3) engage with the private sector early to develop incentives and facilitate processes for quick approval, acquisition, and procurement of rapid point-of-use diagnostics; (4) develop a nationwide distribution plan in coordination with SLTT officials; (5) deploy diagnostics across the country swiftly; (6) make instructions for use easy to understand and less complicated; and (7) simplify reporting to state, local, tribal, and territorial (SLTT) public health and agriculture departments, the Department of Agriculture, DOD, and HHS.

## DETERMINE EFFECTIVE VACCINATION STRATEGIES

Ring vaccination was the strategy of choice during the eradication of smallpox. Believing that all countries had destroyed their stocks of the virus and that there were no longer biological weapons programs anywhere, the plan for ring vaccination remained in place. However, our more recent experiences with COVID-19, pandemic influenza, and other infectious diseases have demonstrated that transportation and population movements cause diseases to spread in different ways than how they behaved in 1980 when the World Health Organization certified the eradication of smallpox. Ring vaccination may or may not work depending on the nature of release and exposure, and today's transportation environment.

The speed at which smallpox would take advantage of global vulnerability to a disease thought to have been eradicated raises doubts about the easy application of old strategies. While we can and should identify and apply lessons learned from previous pandemics and disease events, it is unlikely they will be sufficient to address smallpox. We cannot wait for a smallpox attack or other significant biological event involving orthopoxviruses to occur before we identify other vaccination strategies.

The experience with the 2022 Mpox outbreaks demonstrated that vaccination strategies may need to evolve rapidly and impact available vaccine supply. The ring, or post-exposure prophylaxis vaccination strategy indicated for containing Mpox quickly proved to be ineffective. Given a new mode of transmission of the disease among the most affected populations, a few weeks after the first Mpox case was detected, the CDC recommended pre-exposure vaccination for any individual at high risk of exposure to the disease. Demand suddenly grew and placed additional pressure on vaccine supply. It is conceivable that future outbreaks of smallpox or other orthopoxviruses could display similar changes in transmission patterns, outpacing post-exposure vaccination.

In accordance with Recommendation 22 of the 2015 *National Blueprint for Biodefense*, the Commission recommends the following:

### **RECOMMENDATION 7: Determine most effective vaccination strategies to contain the spread of smallpox and other orthopoxvirus diseases.**

Congress should amend the Pandemic and All-Hazards Preparedness Act (P.L.109-417) to direct the Secretary of Health and Human Services, in coordination with the Secretary of Agriculture, Secretary of Defense, and Secretary of the Interior to (1) engage a Department of Energy national laboratory or laboratory consortium to model the spread of smallpox and other orthopoxvirus diseases in today's immunologically naive environment; (2) direct the CDC to use that model to assess vaccination and other disease response (e.g., pre-exposure vaccination) strategies, using different exposure scenarios and taking into account today's global air and other transit activities; increased population densities and migrations; human-animal interfaces; environmental factors that could impact disease emergence, reemergence, and transmission; mutation; and other factors; and (3) report findings and recommendations to Congress.

## CONTROL AND ELIMINATE DISEASE WHERE BURDEN IS HIGHEST

As the world experienced with Mpox, an emerging infectious disease arising in one continent can spread to rest of the world. Even now, Mpox Clade I is surging in the Democratic Republic of the Congo and Clade II is insufficiently addressed in Nigeria. The fragility of the human-animal disease boundary is more pronounced in developing nations where resources, public health, and animal health infrastructure are particularly limited. Urban areas also become nucleation points for infectious disease risk as their populations grow.

Through the Global Health Security Agenda (GHSA), the United States and its international partners collaborate to reduce biological risk and promote global health security. Launched in 2014 and composed of 70 countries, as well as international organizations, non-governmental organizations, and private sector companies, the GHSA works to prevent, detect, and respond to global public health security threats. US activities include establishing emergency operations centers, strengthening laboratory biosecurity in developing nations, partnering with international health authorities to rapidly detect and manage animal diseases, and implementing and strengthening the International Health Regulations and reporting by the World Health Organization (WHO) and World Organization for Animal Health (WOAH). Multilateral bodies like WHO and WOAH support the development of in-country activities and capabilities to (1) meet international standards for disease control and reporting; (2) prevent cross-border spread of disease; and (3) reduce the risk of accidental and intentional biological threats. However, response capacity comes from nations who agree to make it a priority.

In accordance with Recommendation 33 of the *National Blueprint for Biodefense*, the Commission recommends the following:

### **RECOMMENDATION 8: Proactively engage with other countries and international bodies to strengthen global governance and collective public health response to smallpox and other orthopoxvirus diseases.**

The Secretary of State, in coordination with the Secretary of Agriculture, Secretary of Defense, Secretary of Health and Human Services, and Administrator of the US Agency for International Development, should (1) convene human, animal, food, and environmental health leaders from throughout the world to evaluate current mechanisms, and develop a strategy and implementation plan, for global public health response to biological events involving smallpox and other orthopoxviruses; (2) establish bilateral, multilateral, and other agreements needed to help execute this strategy, and (3) determine how the Biological and Toxin Weapons Convention would apply in the event of a smallpox outbreak anywhere in the world. The Administration and Congress must sustain US financial commitments to international programs that contribute to global health security. The Administration and Congress must also support international institutions such as WHO, WOAH, and World Bank, as well as public-private partnerships like the Coalition for Epidemic Preparedness Innovations.

## DEVELOP A NATIONAL AND GLOBAL HEALTH SECURITY STRATEGY FOR SMALLPOX

Having declared the disease eradicated from the world in 1980,<sup>25</sup> only a few at risk of contracting smallpox are currently vaccinated. However, well-founded concerns about the threatened use of smallpox and the ability for the smallpox vaccine to work against diseases produced by other orthopoxviruses (e.g., Mpox) have resulted in more people in healthcare settings, public health departments, federal law enforcement, military units, and research laboratories getting immunized.

If malevolent actors use weaponized smallpox to attack another nation, the disease will erupt and rapidly spread throughout the world. Previously effective activities to control and eradicate smallpox and other diseases (e.g., contact tracing, movement tracing, ring vaccination, isolation, selective vaccination within 72 hours of contact) will not be sufficient. Additionally, current unknowns about the persistence of contagious virus on surfaces from exfoliated skin, from aerosolized droplets, and by contact with fomites, effective decontamination remains a huge challenge. Our Nation and the world will need a new strategy to overcome and eradicate the disease. As with other pandemics that would impact national security, America will need to leverage all instruments of national power, coordinate across all levels of government and with other countries, and ensure continuity of government, critical infrastructure, and society.

In accordance with Recommendation 3 of the 2015 *National Blueprint for Biodefense*, the Commission recommends the following:

### **RECOMMENDATION 9: Plan in advance to decontaminate, eradicate, and mitigate an attack with smallpox or another devastating orthopoxvirus disease.**

Congress should amend the National Defense Authorization Act to direct the National Security Advisor to produce a National Strategy for Smallpox and Other Orthopoxvirus Diseases and Implementation Plan. The National Security Advisor should direct the White House Office of Pandemic Preparedness and Response Policy, in coordination with the National Security Council Office of Biodefense and Global Health Security, to develop this Strategy to address an attack with smallpox or another devastating orthopoxvirus disease. The objectives of the strategy should be to: (1) determine how the United States will work with other countries to stop, slow, decontaminate, and otherwise limit the spread of a smallpox pandemic to or inside the United States; (2) prevent the domestic and international spread of smallpox disease, suffering, and death; (3) sustain domestic and international critical infrastructure; (4) reduce impact to global and national economies; and (5) ensure national and societal security.

**Table 1. Recommendations for Action by Congress and the Administration**

| RECOMMENDATIONS   | CONGRESS SHOULD...   | FOR ADMINISTRATION ACTION BY...   |
|---|--|---|
| <b>1. Produce biological intelligence</b>                                     | Amend the Intelligence Authorization Act<br>Conduct oversight                                      | The Director of the Central Intelligence Agency, in coordination with the Under Secretary of Defense for Intelligence   |
| <b>2. Get ready to fight and win in biologically contaminated areas</b>       | Amend the National Defense Authorization Act<br>Conduct oversight                                  | Secretary of Defense  |
| <b>3. Evaluate medical countermeasure stockpile needs</b>                     | Conduct oversight  | Secretary of Health and Human Services, in consultation with the Secretary of Agriculture, Secretary of Defense, and Secretary of the Interior  |
| <b>4. Continue diversification of stockpiled medical countermeasures</b>      | Amend the Pandemic and All-Hazards Preparedness Act<br>Conduct oversight<br>Provide appropriations | Secretary of Health and Human Services, in consultation with the Secretary of Defense   |
| <b>5. Develop and obtain broad-spectrum antivirals</b>                        | Conduct oversight<br>Provide appropriations  | Secretary of Health and Human Services, in coordination with the Secretary of Agriculture and Secretary of Defense, and in consultation with the Secretary of the Interior                            |
| <b>6. Develop and obtain point-of-use diagnostics</b>                         | Conduct oversight<br>Provide appropriations  | Secretary of Health and Human Services, in coordination with the Secretary of Agriculture and Secretary of Defense, and in consultation with the Secretary of the Interior                            |
| <b>7. Determine effective vaccination strategies</b>                          | Amend the Pandemic and All-Hazards Preparedness Act<br>Conduct oversight                           | Secretary of Health and Human Services, in coordination with the Secretary of Agriculture, Secretary of Defense, and Secretary of the Interior  |
| <b>8. Control and eliminate disease where burden is highest</b>               | Conduct oversight<br>Provide appropriations  | Secretary of State, in coordination with the Secretary of Agriculture, Secretary of Defense, Secretary of Health and Human Services, and Administrator of the US Agency for International Development |
| <b>9. Develop a national and global health security strategy for smallpox</b> | Amend the National Defense Authorization Act<br>Conduct oversight                                  | National Security Advisor<br>White House Office of Pandemic Preparedness and Response Policy, in coordination with National Security Council Office of Biodefense and Global Health Security          |

# CONCLUSION

The threats from smallpox and other orthopoxviruses are real and credible. The potential consequences of a smallpox attack, or the emergence of another equally deadly orthopoxvirus, are too severe to overlook, especially considering the global population's limited immunity to these diseases. Despite the successful eradication of smallpox, the possibility of its re-emergence, whether naturally or synthetically, demands robust and proactive preventive measures.

The traditional global strategy of reacting to biological events as they occur is not viable for a disease like smallpox. The impact of a third of the US or global population perishing within weeks would be catastrophic, with equally dire implications for our national security and economy.

**There is no benefit in waiting and every reason to act now.** This plan outlines nine actionable recommendations that the Administration and Congress can adopt to significantly mitigate the risk to our Nation and the world. By implementing this plan immediately, we can ensure the continued elimination of smallpox, manage existing orthopoxvirus diseases, and preemptively address others before they emerge. We can box the pox, but to do so, we need to get in the ring today.

# ACRONYMS

|                 |  |
|-----------------|--|
| <b>CDC</b>      | Centers for Disease Control and Prevention                 |
| <b>COVID-19</b> | Coronavirus Disease 2019                                   |
| <b>DNA</b>      | Deoxyribonucleic Acid                                      |
| <b>DOD</b>      | Department of Defense                                      |
| <b>FDA</b>      | Food and Drug Administration                               |
| <b>FSU</b>      | Former Soviet Union  |
| <b>GHSA</b>     | Global Health Security Agenda                              |
| <b>HHS</b>      | Department of Health and Human Services                    |
| <b>IC</b>       | Intelligence Community                                     |
| <b>MCM</b>      | Medical Countermeasures                                    |
| <b>Mpox</b>     | Monkeypox  |
| <b>NATO</b>     | North Atlantic Treaty Organization                         |
| <b>PCR</b>      | Polymerase chain reaction                                  |
| <b>PHEMCE</b>   | Public Health Emergency Medical Countermeasures Enterprise |
| <b>PPE</b>      | Personal Protective Equipment                              |
| <b>SLTT</b>     | State, Local, Tribal, and Territorial                      |
| <b>SNS</b>      | Strategic National Stockpile                               |
| <b>US</b>       | United States  |
| <b>USC</b>      | US Code  |
| <b>WHO</b>      | World Health Organization                                  |
| <b>WOAH</b>     | World Organization for Animal Health                       |

# METHODOLOGY

The Bipartisan Commission on Biodefense was established in 2014 to inform US biodefense and provide recommendations for change. The Commission, supported by academia, foundations, and industry, determines where the United States falls short in addressing biological attacks, accidental releases of pathogens from facilities, and emerging and reemerging naturally occurring infectious diseases that affect national security.

## RESEARCH QUESTIONS

To examine US capability and capacity to defend against smallpox and other orthopoxviruses, we developed the following research questions:

- What is the current orthopoxvirus threat landscape?
- Is the Department of Defense ready to fight against enemies that use biological weapons?
- Is it necessary to evaluate the contents of the national stockpiles of MCM, diagnostic tests, equipment, and effective medical supplies?
- What are the trade-offs between safety and effectiveness when considering the possibility of attacks versus naturally occurring disease events?
- Do we need new vaccination strategies, in addition to ring vaccination?
- Should biological attacks using weaponized smallpox occur, how can we plan to eradicate the disease again thereafter?
- Should more countries than the United States and Russia possess smallpox?

## PRELIMINARY RESEARCH

The Commission reviewed previous research efforts; scientific studies; and previous and more recent federal strategies, plans, funding, and research and development programs related to defense against orthopoxvirus threats and catastrophic risks. This review allowed for an assessment of the comprehensiveness and effectiveness of biodefense in this regard.

## ANALYSIS

Staff synthesized and evaluated ideas, feedback and suggestions given, alongside individual expert interviews and literature review, to help inform the development of this plan. Staff evaluated findings and recommendations considering the Commissioners' own experiences. Staff did not use quantitative methods for this analysis.

## LIMITATIONS

Several biodefense programs and policies; intelligence, raw data, and documents; appropriations and budget documents; and other sensitive information are classified or otherwise unavailable. The Commission did not review these materials.



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<sup>13</sup> This activity should consider the possibility that some of the tons of previously weaponized smallpox might have been moved to other locations in Russia before destruction and remediation of original locations for the material.

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