LAUNCH & SCALE SPEEDOMETER

Issue Brief – Monkeypox: Recent Developments in the Outbreak and Lessons from the COVID-19 Pandemic

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2022 Monkeypox Outbreak and Control: Overview

Monkeypox, a viral infection in the same family as smallpox (orthopoxviruses) that is endemic to West and Central Africa, has seen an outbreak in non-endemic countries, including across Europe and North America, with cases identified beginning in May 2022. On July 23, 2022, the WHO declared the monkeypox outbreak a Public Health Emergency of International Concern (PHEIC) after a second meeting of the International Health Regulations Emergency Committee. At the emergence of the outbreak, cases were noted to be mainly, though not exclusively, among men who have sex with men (MSM) (WHO). As of August 25, 2022, 46,337 cases of monkeypox have been reported in 91 non-endemic countries, including 16,925 in the US, 17,202 in the EU, 3,207 in the United Kingdom, and 1,206 in Canada (CDC, ECDC).

Monkeypox can be transmitted from animals to humans as well as from humans to humans from contact with bodily fluids or skin lesions, often from close, skin-to-skin contact: most cases have been linked to sexual contact, although monkeypox may also be transmitted during other instances of close contact. The incubation period can range from 5 to 21 days. The disease is characterized by skin lesions; other symptoms include fever, chills, headaches, muscle aches, and swollen lymph nodes. Health care professionals can identify monkeypox with a PCR test of a sample of fluid swabbed from a lesion.

Vaccines and therapeutics originally developed for smallpox can be used effectively for the prevention and treatment of monkeypox. In contrast to COVID-19 vaccines, the monkeypox vaccine can be effective when administered after exposure to the virus (as post-exposure prophylaxis), and vaccination strategy represents a critical opportunity as countries seek to contain the monkeypox outbreak and protect their populations. However, critical barriers have blocked the rollout of those containment approaches. As the situation continues to evolve, the monkeypox outbreak presents an opportunity to apply key lessons from the COVID-19 pandemic and respond to this outbreak more efficiently, effectively, and equitably.

In this brief, we highlight the challenges in controlling the monkeypox outbreak in global and US contexts and provide practical recommendations and lessons from the COVID-19 pandemic. This issue brief will focus primarily on analysis of the monkeypox vaccine marketplace as an urgent and pressing challenge.

Monkeypox Vaccine Marketplace

Vaccines for smallpox have been shown to be about 85% effective against monkeypox, and in response to the recent outbreak, several countries reacted rapidly, purchasing additional supplies. Although clinical data for the efficacy and safety of using these vaccines in preventing monkeypox is not available yet, two vaccines have been used or considered for monkeypox by many countries including US and countries in the European Union.

- MVA-BN is a smallpox vaccine manufactured by Danish company Bavarian Nordic (marketed as JYNNEOS in the US, Imnavex in Europe, and Invamune in Canada) and

initiating vaccination campaigns for close contacts of confirmed cases and at-risk populations. One course of the vaccine consists of two doses administered four weeks apart.

- ACAM2000 is an older, second-generation smallpox vaccine. It can have greater side effects, so there are more safety concerns around its use. ACAM2000 requires one dose and is administered via skin punctures with a forked needle that form a lesion.

Global Context of the Monkeypox Outbreak

An August 24 situation report from the WHO states that the number of monkeypox cases reported globally for the week of August 15-21 decreased by 21% compared to the previous week, in contrast to the previous trend of four consecutive weeks of increases in cases. The report notes that the overall decrease in new cases may be driven by a decrease in cases in Europe. However, the number of cases reported in the Americas continues to rise steeply. Out of all the countries reporting cases, the US reported the highest increase in weekly number of cases. The US has also reported the highest cumulative number of cases globally.

2.4 million doses of earlier generation smallpox vaccines are held physically at the WHO in Switzerland, and 31 million doses of newer vaccines were pledged by five WHO member states (France, Germany, New Zealand, the UK, and the US) in 2005 to prepare for potential future smallpox outbreaks. However, the WHO needs to make an informed decision on which vaccines should be used under what situation, and it is unclear whether the current monkeypox outbreak can trigger access to the stockpiles. These doses have also not been distributed to African countries to combat monkeypox despite cases rising in the region in the years since the conclusion of the global vaccination campaign to eradicate smallpox in 1980. Countries in Central and West Africa where the disease is endemic have generally maintained only small stockpiles of vaccines to administer to healthcare workers in the case of outbreaks. Despite increasing numbers of monkeypox cases in the region since the 1980s as smallpox immunity has waned, there have not been major efforts to combat the virus in endemic countries.

As countries continue to place large vaccine orders, **Bavarian Nordic's manufacturing capacity may present further challenges**: the company noted that it can manufacture 30 million vaccine doses per year (including all the vaccines it makes, not solely MVA-BN) and is uncertain that it can meet global demand for the vaccine. The US Department of Health and Human Services (HHS) has facilitated an agreement between Bavarian Nordic and Grand River Aseptic Manufacturing (GRAM), a US-based pharmaceutical contract manufacturer, to establish the first fill and finish line for the MVA-BN vaccine in the US. Fill and finish is the final manufacturing phase to turn bulk vaccine into usable doses. This agreement was made under US's procurement deals with Bavarian Nordic, and it is not clear if Bavarian Nordic would make similar arrangements with other countries to expand its production capacity.

As countries rush to procure enough vaccine doses to vaccinate their populations, low- and middle-income countries (LMICs), especially countries in Central and West Africa where monkeypox is endemic, are at risk of being left behind.

> *High-income countries have placed large procurement orders for monkeypox vaccines and treatments.* The US also signed multiple procurement orders in June and July, purchasing a total of 5.5 million doses in 2022. The EU purchased about 110,000 doses of MVA-BN in June and another 54,000 in July to distribute among its member states, the UK purchased a total of 150,000 doses, and Canada signed a $56M deal with Bavarian Nordic for supplies of the vaccine.
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> On June 23, 2022, SIGA announced an additional $11M of initial procurement orders for its antiviral treatment from "two new international jurisdictions," one in Europe and one in the Asia Pacific Region, noting that these orders were "directly in response to the evolving global monkeypox outbreak."

In the context of the global threat presented by the monkeypox outbreak, **vaccine nationalism** may hinder the coordinated international efforts needed to reign in the outbreak and control the global spread of the virus. Additionally, as the outbreak spreads, countries may compete for resources, and similar to export restrictions seen with COVID vaccines, some experts have warned that the EU could ban exports of MVA-BN, thus limiting shipments of the vaccine abroad and creating further access challenges.

Local manufacturing capacity has been highly correlated to earlier access to life-saving health interventions, as demonstrated with COVID-19 vaccines. Besides China and India, which both had strong vaccine manufacturing capacity before the pandemic, many LMICs planned to build vaccine manufacture capacities, such as the Partnership for African Vaccine Manufacturing (PAVM) launched by Africa CDC and Africa Union. However, key actions are still needed to grow LMIC-based manufacturing capacity including further public and private investment, voluntary licensing agreements, transfer of know-how, capacity strengthening, and regulatory supports.

The Monkeypox Outbreak and Control in the United States

On August 4, the US declared the monkeypox outbreak a Public Health Emergency (PHE), which will allow the government to further mobilize resources and bolster current response efforts. This declaration comes at a critical time for the US government as it continues to face criticism about response efforts thus far.

As of August 25, cases have been reported in all 50 states across the US, with a total of 16,925 confirmed monkeypox cases. The outbreak has spread rapidly in the US: in early July, there were about 500 cases reported, and by early August, the case total had jumped to nearly 7,000. Cases have primarily been reported in men, with the plurality in the 31-35 age group (CDC).

Testing challenges: The number of monkeypox cases in the United States is very likely higher than reported, as several sources have noted the lack of testing due to narrow eligibility criteria at the beginning of the outbreak in May. This situation is similar to the early stages of the COVID-19 pandemic in 2020, when undertesting led to underestimations of COVID-19 cases and community transmission as infected people spread the virus unknowingly. The CDC set up monkeypox testing in public health labs across the country in May, but the procedure to obtain a test was often cumbersome and time-consuming, making it difficult for doctors to order tests for their patients.

In June, the CDC began shipping tests to five commercial laboratory testing companies in an effort to increase testing capacity and access across the country. This expansion to include commercial labs is estimated to increase testing capacity from the 6,000 tests per week initially available through the government-run public health Laboratory Response Network (LRN) to 60,000 to 80,000 tests per week. In June and July, the CDC also expanded the case definitions for monkeypox to create increased avenues for suspected monkeypox cases to be tested.

Vaccine shortage:

- **Market authorization:** MVA-BN was already approved for use against monkeypox by the US FDA. MVA-BN is the preferred option for vaccination, recommended by the CDC as post-exposure prophylaxis for healthcare workers and others who have been exposed and as pre-exposure prophylaxis in at-risk populations. Despite existing regulatory approval for MVA-BN in the United States prior to the outbreak, delivery of the vaccine to at-risk populations has fallen short, with individuals across the country facing challenges getting vaccinated. Rollout of COVID-19 vaccines in 2021, following successful development and approval in late 2020, was similarly hindered by shortages and slow distribution.

- **Procurement and supply:** In early June, the US ordered 500,000 doses of MVA-BN, to be delivered later this year, to supplement an existing stockpile of 72,000 doses that are on hand. In July, the US placed two more orders for 2.5 million doses each. In total, the US owns nearly 7 million doses of the MVA-BN vaccine, including the three orders from this year and an order for 1.4 million doses from 2020, though the majority of those doses have not yet been delivered and are thus not available for distribution yet. An additional 786,000 doses have become available following the FDA's inspection and approval of a vaccine manufacturing plant in Denmark in late July. Following these additional orders from the US government, Bavarian Nordic expanded its manufacturing capacity to allow orders to be filled by a US-based manufacturer and estimates that 1 million doses will be delivered in 2022.

  The US has 100 million doses of ACAM2000 on hand as part of the strategic national stockpile maintained for use in the case of future smallpox outbreaks, in part motivated

by the bioterrorism threat of the virus (smallpox was eradicated in 1980, but both the United States and Russia currently hold live samples of the virus).

Although the United States has purchased large quantities of the vaccine in response to the outbreak, in addition to previously purchased doses as part of the national stockpile, the government has far fewer doses on hand than are purchased in total, since orders take several months to fill as the vaccines are manufactured and required inspections are carried out by the FDA before doses can begin to be distributed in the US.

- **Distribution and vaccination:** As part of the ongoing nationwide vaccination strategy, the US Government is allocating and distributing supplies of MVA-BN to states and jurisdictions based on the number of at-risk individuals, case burden, and transmission rates in those areas, with the goal of prioritizing areas where the outbreak has been more severe. In response to ongoing shortages of the vaccine, on August 9 the FDA issued an emergency use authorization (EUA) for MVA-BN to be administered in smaller doses, in an attempt to stretch the limited number of doses to reach more people. These smaller doses, about one-fifth of a full dose, must be administered intradermally, a technique that requires more training in comparison to the current method of subcutaneous injection, and although this authorization will increase the number of available doses by "up to five fold," evidence for this technique's effectiveness is limited to data from one study. Under this new strategy, people will still need two doses of the vaccine.

Treatments for Monkeypox: Monkeypox treatment options include antiviral medications for smallpox: TPOXX (tecovirimat) and Tembexa (brincidofovir) are approved by the FDA for treatment of smallpox and may be used to treat monkeypox. In the US, tecovirimat is available from the strategic national stockpile, but brincidofovir is not. The US currently has a stockpile of 1.7 million doses of tecovirimat and ordered up to $7.5M of tecovirimat in May 2022 from manufacturer SIGA Technologies, with $3.6M planned for delivery in 2022. In the US, tecovirimat is available for monkeypox through the CDC's non-research expanded access Investigational New Drug protocol (EA-IND), to which providers must apply through a potentially lengthy process. Although there are no known naturally occurring resistances to tecovirimat, the drug has a low resistance barrier, which means that it is relatively easy for mutations in the virus to lead to resistance to the treatment.

Moving forward

As the monkeypox outbreak continues to spread, stronger, more coordinated international action is required to limit further spread, prevent the virus from potentially becoming endemic in new regions, and proactively combat the emergence of new variants. The current situation presents an opportunity to reflect and learn from experiences responding to the COVID-19

pandemic and approach this outbreak with an eye towards global health equity and future pandemic preparedness. Recommendations for responding to the monkeypox outbreak include:

- To understand the scale of the outbreak and respond to it promptly, **countries must quickly scale up accurate diagnostics**. So far in the United States, we have not seen sufficient widespread availability of monkeypox testing, and as a result there is not a clear picture of the number of cases. During the COVID-19 pandemic, tests were not immediately available and had to be developed before then being made widely available, creating a delay in our understanding of the extent of the spread of COVID-19. In the case of this monkeypox outbreak, tests existed from the outset, but bottlenecks have still limited the extent of testing, opening the door for further community transmission and underrepresentation of the actual number of cases.
- As countries move to procure vaccines for their own populations, **the consequences of vaccine nationalism threaten to widen inequities and lead to worse overall global outcomes**, as seen throughout the COVID-19 pandemic: disparities in access to COVID-19 vaccines between high-income countries and LMICs have weakened efforts toward an effective global response, creating greater risk of new variants emerging. **As a global health threat, the monkeypox outbreak requires coordinated global efforts to combat and contain, including equitable distribution of vaccines and treatments.**
- Smallpox vaccine development used a prototypic vaccine approach against pathogens from an entire genus of viruses, which is how smallpox vaccines are able to protect against all known orthopoxviruses, including monkeypox (CEPI). We are seeing the benefit of that approach now as smallpox vaccine supplies are being mobilized in response to the monkeypox outbreak. Going forward, **employing a prototypic vaccine development approach that targets groups of pathogens rather than individual strains can improve preparedness for future pandemics and proactively provide the tools needed to combat them**.

About the Launch and Scale Speedometer

The Launch and Scale Speedometer aims to systematically analyze the factors that support or hinder the introduction and scaling of interventions, including but not limited to drugs, diagnostics, and devices, to address critical global health challenges. The Launch and Scale Speedometer is led by the Duke Global Health Innovation Center. Find out more: https://launchandscalefaster.org/about

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