

Monkeypox: balancing response and future preparedness during a global public health emergency

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While the recent data on declining cases is good news, the monkeypox response, regrettably, exemplifies what being unprepared for a public health emergency (PHE) looks like in practice. There are currently limited and suboptimal vaccines, diagnostics and therapeutics. There is just one vaccine licensed against monkeypox, a live attenuated vaccine, that uses a non-replicating Modified Vaccinia Ankara virus platform from Bavarian Nordic (MVA-BN). This vaccine currently has limited availability, no clinical data to demonstrate its efficacy in women and children, and question marks around its real-world effectiveness.¹ The live replicating smallpox vaccines which represent second and third choice options (ACAM2000, LC16m8) are inconvenient to administer, have less than ideal side effect profiles, and also lack human clinical data to prove their worth in fighting monkeypox.² In the case of diagnostics, there are confirmatory molecular tests available, but these do not have necessary stamps of approval or emergency use authorisations from any Stringent Regulatory Authority or WHO. And there is only a single antiviral treatment (Tecovirimat also known as TPOXX)—this is not formally licensed for monkeypox, rather it's available for investigational/compassionate use, again based on non-human studies.³

The dire situation for medical countermeasures (MCMs) serves as a useful case study to explore the fundamental challenges the world faces in being prepared for difficult-to-predict outbreaks of novel and rare pathogens—one of the 2022's biggest public health priorities following the COVID-19 pandemic.

Monkeypox is not novel—the world has known about the virus's potential to affect humans for over 50 years. But it is rare: there have been very limited cases before 2022, and almost all in West and Central Africa. This, combined with the low fatality rates drives low demand for MCMs. In turn, there are limited

SUMMARY BOX

- ⇒ The current monkeypox response, regrettably, exemplifies what being unprepared for a public health emergency (PHE) looks like.
- ⇒ There is just one vaccine licensed against monkeypox, with limited availability, no clinical data to demonstrate its efficacy and questions around its real-world effectiveness. There are confirmatory molecular tests for diagnosis, but these do not have necessary stamps of approval from any Stringent Regulatory Authority or WHO. And there is one antiviral treatment: this is not even formally licensed for monkeypox, but available for compassionate use based on non-human studies.
- ⇒ We consider how the world might respond to a PHE while simultaneously supporting preparedness for the next one—outbreak preparedness being one of the biggest global health priorities of 2022. While the global public health community might like to do everything to prepare for the worst and to respond now with full force, budgets are usually constrained, and so choices must be made.
- ⇒ To do better we must first build on the existing high risk pathogen prioritisation frameworks, checking that resources are targeted appropriately and advocating for change where they are not. Second, within each pathogen, viral family, or other disease-outbreak archetype, we must attempt to prioritise in advance the R&D and supply investments for preparedness and response. Third, we must put in place the appropriate tactics against these priorities.
- ⇒ By doing this, we can use the monkeypox response to create a template for improving preparedness through response. The range of other pathogens where there are gaps in our armoury of countermeasures is large—so we will have to wrestle with these questions and trade-offs again.

incentives for companies to conduct research and development (R&D) or pursue licensure, or for donors to subsidise these. Even the one licensed monkeypox vaccine is a byproduct of the 'Animal Rule' regulatory approval pathway in which a smallpox vaccine was tested in animal models against monkeypox. In short, no one initially explicitly set out to



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make a licensed monkeypox vaccine. Part of the reason for this is that past outbreaks have fizzled out, making it difficult for developers to conduct the rigorous, large clinical trials on safety and efficacy—which are usually needed to secure regulatory approval of vaccines and therapeutics.

At UNICEF's Supply Division, we work to expand access to broad range of vaccines, medicines, diagnostics, and ancillary medical supplies, as well as products to improve nutrition, sanitation, hygiene, education and much more. As part of this, we work closely with our partners to ensure low-income and middle-income countries have resilient social systems and can prepare for, respond to, and recover from PHEs. The announcement to classify the current monkeypox outbreak as a Public Health Emergency of International Concern (PHEIC) is helpful because it accelerates a range of necessary actions to deal with the situation.⁴ For example, UNICEF is working closely with WHO in planning for a potential vaccine access programme. We are working with WHO, donors, and manufacturers to ensure: there are routes of access to existing vaccines (primarily through donation programmes); there are syringes to accompany the doses; there is an allocation mechanism for equitable access if demand outstrips supply; that indemnity and liability (I&L) is agreed if needed; freight and logistics are planned; and other essential steps are taken to facilitate access. We're also engaging with diagnostics manufacturers now to ensure we can buy diagnostic testing kits as soon as these receive regulatory approval and countries tell us how much of which tests they want.

In parallel, UNICEF is working with WHO and other partners to refine how we can respond to PHEs now and in future. In a white paper, the WHO Director-General underscored the need to 'Expand partnerships for a whole-of-society approach for collaborative surveillance, community protection, clinical care and access to countermeasures' as one of 10 proposals to strengthen health emergency preparedness, response and resilience.⁵

Reflecting on the current state of monkeypox MCMs and the Temporary Recommendations issued by the WHO Director-General, it is important to draw out that R&D and supply planning are both central to this PHE response. A list of desired developments might include better MCMs (particularly vaccines); data to validate the use of existing MCMs; data to inform new/different uses of existing MCMs (e.g., fractional dosing and/or more convenient dosing regimens); greater production capacity of existing MCMs (particularly vaccines and therapeutics); stronger systems to make better use of the existing MCMs (particularly vaccines); and perhaps reducing commercial barriers to access (e.g., affordable pricing, agreed and funded means for dealing with I&L,...) across existing and future MCMs. Some of this is well underway, for example in the form of trials to evaluate existing vaccines or novel dosing of these vaccines, and trials to evaluate existing therapeutics, and work by

WHO Collaborating Laboratories to validate molecular diagnostics.^{6–10}

But, in our collective scramble to respond now to the monkeypox PHE, we must try to make smart decisions today that will support wider, future preparedness. Trade-offs do exist between many of the elements on the above list, and none of them are easy. We highlight three below:

1. How much delay or extra cost is tolerable to respond in a way that supports future preparedness? The current live attenuated non-replicating monkeypox vaccine (i.e., MVA-BN) is available in very limited quantities. A health-maximising approach would take this limited supply and target populations most at risk of severe disease and death as soon as possible. By contrast, responding in a way that generates data to inform future regulatory decisions and normative guidance at times may be slower and more costly. For example, the available monkeypox vaccine requires a long gap (6 weeks) between the first and second dose, which may lead to high drop-out rates especially in resource-poor settings. So, should the global response prioritise funding of trials to collect data on new and more convenient dosing regimens, or simply focus on getting the limited supply to those most vulnerable as soon as possible? While the former is described in the temporary recommendations issued by WHO, arguably, many High-Income Countries (HICs) are taking an approach more akin to the latter.

2. When do you invest in 'better' products, versus in more effective use of the existing and suboptimal products? The live replicating smallpox vaccines (i.e., ACAM2000, and LC16m8) that might be used against monkeypox have less favourable safety profiles than MVA-BN. What's more, these smallpox vaccines require a unique bifurcated needle to facilitate scarification of the skin, a technique barely used today. Should global funders focus on scaling up production of the safer and easier-to-administer product to reduce health risks, reduce health worker training needs and minimise delivery hassles? Or should we focus on training health workers to allow for these potentially 'second best' vaccines where supply might be looser? Will this training have any preparedness value in the longer term?

Another variant of this product versus delivery question could equally apply to the approved monkeypox vaccine: do you invest in trials of the new dosing regimens (as above); or fund strengthening of the health system to better reach, track and reaccess people for their second dose?

3. Third, how should the global community seek to balance long term commercial viability and sustainability (which drives R&D) investment) with acute pressures to reduce burden as equitably as possible when an outbreak happens. Now monkeypox is a large-scale PHE, it might be tempting to push for the vaccine and therapeutic manufacturers to reduce their prices, and/or share the intellectual property or technology needed to make these products.¹¹ However, it can be easy to forget that the monkeypox vaccine and the sole therapeutic are

each owned by small companies, who have maintained the products despite virtually non-existent demand for years. How the world seeks to address access today sends important signals to private actors about future investment in MCMs for the next PHE.

For at least the first two questions, it is tempting to want to do all of these things simultaneously or suggest that the above represent false choices. However, the incidence of the disease does limit the scope for research (outbreaks can be too small for good research—as previous monkeypox ones have). Even the biggest monkeypox outbreak is limited in scale as compared with an airborne and highly transmissible virus like SARS-CoV-2); and of course, funds are not infinite. Alternatively, it is tempting to want to do all of the above, but at different times—for example, investing in research now and investing in systems to deliver suboptimal products later, only if we don't succeed in creating better products, or if we can't scale up production of favoured products soon enough. But, as the world learnt from COVID-19, unless commensurate efforts are put into both R&D and delivery systems, the resultant rollout will be hampered by system constraints.

There are other important lessons from prior PHEIC responses that may be instructive as we grapple with these questions. During the 2016 Zika Virus (ZIKV) PHEIC, UNICEF supported the development and validation of point of care rapid diagnostic tests for ZIKV (tools which do not exist for monkeypox).^{12,13} However, since they were developed there has not been a significant ZIKV outbreak where they have been needed. Something similar happened with Ebola diagnostics: these were commercialised during the 2014–2015 PHEIC, but then the manufacturers exited the market due to low/no demand in subsequent years.¹⁴ Given that monkeypox cases are currently dropping, there is a risk that we end up in a similar situation here. Looking at more positive examples, the major investments in national level diagnostic capacities as part of the COVID-19 response are understood to have paid dividends for monkeypox: more laboratories in Africa operating at higher volumes and standards.¹⁵

Prior to a PHE, and in the absence of budgetary and political constraints, preparedness efforts might see country governments and international and global health actors such as WHO, UNICEF, the World Bank, Gavi—the vaccine Alliance, and the Coalition for Epidemic Preparedness Innovations (CEPI), collectively working to prepare for the worst while hoping for the best. But preparedness is not free, and the 'returns' (both health and financial) can vary from awful to astronomical, depending on what one decides to count and exclude, and the time frame over which one accounts for these future returns. As the world came to understand during the COVID-19 pandemic, responding to a large outbreak is complex and fraught with challenges. Trying to respond to such PHEs while simultaneously attempting to be better prepared for the next one is

even harder. To do better, we need three things—none of them easy.

- I. First, update and build on the existing high-risk pathogen prioritisation frameworks (e.g., developed under the auspices of the WHO R&D Blueprint, the National Institute of Allergy and Infectious Diseases, the European Commission's Health Emergency Preparedness and Response Authority, and the UK Vaccine Network), checking that resources are targeted appropriately, and advocating for change where they are not.
- II. Second, within each pathogen, viral family, or other disease-outbreak archetype, start to prioritise in advance the supply investments for preparedness and response. This involves grappling with the questions above, but also questions like 'How big is the R&D gap between the products we have, and the products we want?', 'Will we accept good immunogenicity data (in lieu of human clinical efficacy data) in an emergency?' and perhaps more controversially 'How likely is it that the perceived risk to HICs from this pathogen will lead them to lock up or hoard supply?'. Sharper prioritisation of what to do in advance should move us away from today's ad hoc, time and donor-dollar-based prioritisation approaches that are encompassed within the broad guidance from WHO and others.
- III. Third, put in place the appropriate tactics against these priorities, for example, a predesigned and funded clinical trial waiting for an outbreak to recruit participants and collect human efficacy data, a conditional technology transfer agreement to scale up production capacity, rotating global stockpiles of countermeasures such as personal protective equipment (PPE) and/or ancillary equipment such as syringes.

Sharp prioritisation is very difficult when faced with large uncertainties, varied and implicit conceptions of 'returns', and diverse, political stakeholder groups. WHO can and will lead, and coordinate, much of this but tackling some of the questions above may require judicious use of expert groups and other tools to trim down 'prioritised' long-lists. Without taking such tough choices, the risk is that we do not prioritise, or we prioritise everything—thereby leaving actual prioritisation to those who control the purse strings (e.g., HIC governments). Such reliance on decisions and actions taken by a few HICs may lead us down a pathway to towards the likes of vaccine nationalism.

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