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Review Article

The Human Mpox Global Outbreak: Available Control Tools and the Opportunity to Break a Cycle of Neglect in Endemic Countries

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Abstract. The 2022 global outbreak of human Mpox (formerly monkeypox) virus (MPXV) infection outside of the usual endemic zones in Africa challenged our understanding of the virus's natural history, transmission dynamics, and risk factors. This outbreak has highlighted the need for diagnostics, vaccines, therapeutics, and implementation research, all of which require more substantial investments in equitable collaborative partnerships. Global multidisciplinary networks need to tackle MPXV and other neglected emerging and reemerging zoonotic pathogens to address them locally and prevent or quickly control their worldwide spread. Political endorsement from individual countries and financial commitments to maintain control efforts will be essential for long-term sustainability.

According to a World Health Organization (WHO) report published on July 23, 2022, the current global outbreak of human Mpox (formerly monkeypox) is considered a public health emergency of international concern.[1] Mpox is a viral zoonotic disease that was first reported in 1958 during an outbreak at a Danish laboratory among monkeys imported from Singapore.[2] It was recognized as a human disease in 1970, when a 9-month-old child was diagnosed in the village of Basankusu of Equateur Province in the Democratic Republic of the Congo (DRC).[3] Mpox virus (MPXV) is an enveloped double-stranded DNA virus that belongs to the Orthopoxvirus genus of the Poxviridae family, and is typically found in the tropical rainforests of West and Central Africa.[4,5] There are two distinct genetic clades: Central African (Congo Basin; clade I) and West African (clade II). Experts have since reached a consensus to subdivide clade II into clades IIa and IIb, with the latter encompassing the subclade found east of the Dahomey Gap in West Africa, and of which the lineage B1 is responsible for the 2022 global outbreak.[6]

Although the actual MPXV reservoir remains elusive, African rodents (e.g., squirrels and rats) are thought to be the most likely reservoir, and the virus has also been found in other animals (e.g., shrews).[7,8] Nonhuman primates are only transiently infected with MPXV and are therefore potential intermediate hosts but not reservoirs.[9] This fact, combined with stigmatizing connotations, suggests that "monkeypox" was an inappropriate name, leading to the recent renaming of the syndrome as "Mpox."[10,11] MPXV can be transmitted to humans via close contact with infected animals via bodily fluids (saliva, respiratory secretions, or blood), contact with mucosal lesions, or exposure to contaminated material during meat preparation. Prior to the 2022 outbreak, human-to-human transmission was best documented for clade I. Transmission has been steadily increasing, coincident with the waning of smallpox immunity. In the 1970s, the estimated secondary attack rate among household contacts was as low as 8%,[12] but in a recent outbreak a secondary attack rate of 50% was reported.[13] Although previously not well documented, human-to-human transmission might be even more pronounced for clade II. In 2017, Nigeria faced a large outbreak of clade IIb MPXV infection after decades of relative absence of the virus. Importantly, during this outbreak, only a minority of patients reported contact with wildlife, outbreaks were reported in prisons, and strong clustering was noted within households.[14] Moreover, genomic changes in the virus mediated by host enzymes suggest prolonged circulation within the human population.[6] Over the last decade, Central and West African countries have reported thousands of suspected Mpox cases, resulting in hundreds of deaths every year. These numbers have been steadily increasing, with a case-fatality rate of up to 11% for clade I but less than 1% for clade II.[3,4,15] In the DRC, the nation with the highest annual numbers of suspected MPXV infections, Mpox cases have increased from around 500 per year in the 1990s to

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10,545 reported/suspected cases and 362 deaths from January 2020 to July 2022.[5,16–18] The median age at presentation has increased from 4 (1970s) to 21 (2010–2019) years, with ≥50% seen in males.[19] Unfortunately, because of a lack of systematic investigation within the DRC, most suspected cases are not tested and are therefore not represented in official WHO reports, which include only confirmed cases.[15]

The ongoing Mpox outbreaks outside of endemic zones have challenged our understanding of the dynamics of MPXV transmission and the evolving epidemiological characteristics of the disease.[20] Clade IIb was documented for the first time in 2017 from Nigeria, only to emerge 5 years later around the world. How exactly clade IIb was able to spread so widely remains to be investigated, but genetic analyses indicate that the variant that caused the 2022 global outbreak is closely related to strains isolated in Nigeria in 2017 and therefore circulating among humans for several years.[6,21,22] It is therefore possible that if more attention had been given to the 2017 outbreak in Nigeria, the global spread of Mpox could have been averted.

Most Mpox cases in Europe and the United States in 2022 exhibited a different clinical presentation from cases in West and Central Africa and were documented primarily among adults who self-identify as men who have sex with men. For confirmed cases in the United Kingdom with available gender information, 1,033 (99.5%) were in males and 5 were in females, with a median age of 36 years.[23] In endemic African countries, Mpox typically presents with a prodromal febrile phase followed by pronounced lymphadenopathy and a generalized centrifugally spreading rash. The disease is often accompanied by complications including sepsis, multiple organ failure, bacterial superinfection, eye infections, and abortion or stillbirth.[24] In contrast, in the 2022 global outbreak, skin lesions were more localized, and generalized symptoms were often absent[25,26]; numerous asymptomatic cases were described.[27] Mucosal involvement also appeared to be more common in the recent outbreak than previously described, frequently leading to proctitis, urogenital symptoms, and tonsillitis. Fortunately, the mortality in this outbreak was low, with only a few reported deaths, mostly in severely immunocompromised patients.[25]

The reasons for differences in disease expression for two MPXV clades in two different epidemiological settings remain unknown. Potential explanations include differences in pathogenicity of viral clades, epidemiological features of affected populations, and access to hygiene relevant to viral spread. In a preclinical mouse model, infection with clade I MPXV led to more severe disease compared with clade II and especially with clade IIb.[28] Isolates circulating during the 2022 outbreak accumulated 46 mutations compared with the clade IIb MPXV strains isolated in 2018, of which many were probably caused by the host enzyme APOBEC3 and the result of prolonged human-to-human transmission.[29] These mutations may have given rise to a less virulent virus better adapted to the human host. In addition, differences in disease expression may have been influenced by different modes of human-to-human transmission, namely mucosal inoculation during sexual contact in the 2022 global outbreak versus inhalation during household contact in endemic settings. Inhalation of viral particles may lead to more pronounced viremia, resulting in dissemination, rather than the localized disease seen after mucosal inoculation.

Two vaccines may be used for the prevention of Mpox (Table 1). Both were developed against Variola virus, the causative agent of smallpox, and are based on the attenuated Vaccinia virus, which induces cross-protection against both Variola virus and MPXV. The second-generation smallpox vaccine ACAM2000 (a live, replication-competent Vaccinia virus vaccine) has been approved for immunization against smallpox (Strategic National Stockpile [SNS] use only) and made available for use against Mpox under an Expanded Access Investigational New Drug (EA-IND) protocol. ACAM2000 has a high potential for side effects and has therefore been in limited use despite ample supply. Third-generation smallpox vaccines (e.g., Jynneos, Imvamune, and Imvanex) make use of the modified Vaccinia Ankara strain, a live vector for which replication is impaired in most mammalian cells. Jynneos is approved by the Food and Drug Administration (FDA) for the prevention of Mpox and smallpox and is safe for use in immunocompromised people. Because of the limited availability of Jynneos, the Centers for Disease Control and Prevention (CDC) recommend prioritizing its use for people at risk for either severe ACAM2000 side effects or severe disease from MPXV infection (e.g., people living with HIV or with other immune deficiencies). As postexposure prophylaxis, vaccination against MPXV needs to be within 3–4 days of virus exposure to confer protection against the disease and severe symptoms.

Three antivirals are currently available as potential Mpox treatments (Table 2). These antivirals are not approved specifically for use against MPXV infections but have been developed as therapies for smallpox in the event of a reemergence. Oral brincidofovir (also known as CMX001 or Tembexa), a lipid-conjugated prodrug of cidofovir, was approved in 2021 by the FDA to treat smallpox in adult and pediatric patients. Although no data are available on the effectiveness of brincidofovir in

TABLE 1
Potential vaccines for the prevention of human Mpox disease[36]

Name	Source	Regulatory aspects	Efficacy and safety profile	Availability
ACAM2000 vaccine	Second generation: cell culture derived	Approved for immunization against smallpox disease and made available for use against Mpox under an Expanded Access Investigational New Drug protocol	Replaced Dryvax first-generation vaccine in 2007 but has contraindications + adverse events	Yes
Jynneos vaccine (Imvamune or Imvanex)	Third generation: replication-deficient strains	Food and Drug Administration approved for prevention of smallpox and Mpox	Good results in clinical trials; no adverse events reported, immune responses similar to ACAM2000	Yes

TABLE 2
Potential therapeutics for human Mpox virus[36]

Name	Mechanism of action	Regulatory aspects	Efficacy evidence	Availability in strategic stockpile
Tecovirimat (TPOXX or ST-246)	Interferes with the maturation and release of Orthopoxvirus from infected cells by inhibiting p37 envelope-wrapping protein	Approved by the US FDA in 2018 ("animal rule"); in Europe in 2022 and Canada in 2022 for Orthopoxvirus-associated infections in outbreaks	Effective in treating disease caused by orthopoxviruses in different animal models, but no human clinical data are available	Yes
Brincidofovir (BCV, CMX 001, or Tembexa)	Lipid-conjugated prodrug of cidofovir and inhibitor of DNA polymerase	Approved by the US FDA but not in Europe for treatment of smallpox in 2021	No clinical efficacy data are available but is proved effective against orthopoxviruses in several in vitro and animal studies	No
Cidofivir (CDV)	Inhibitor of DNA polymerase	Approved in the United States and Europe for treatment of cytomegalovirus retinitis in AIDS patients with normal renal function only; available via the Investigational New Drug protocol for smallpox treatment	Activity against proviruses from in vitro and animal models	Yes

FDA = Food and Drug Administration.

treating human Mpox, it proved effective against orthopoxviruses in several in vitro and animal studies. Presently, the CDC is developing an EA-IND application to facilitate the use of brincidofovir as an Mpox treatment, although the drug is not currently available from the SNS. Intravenous cidofovir (also known as Vistide) received approval by the FDA to treat AIDS-related cytomegalovirus retinitis in 1996, but the drug has also been used in various formulations for off-label treatment of serious diseases caused by DNA viruses because of its broad-spectrum activity. Cidofovir has not been approved by the FDA for smallpox treatment, but it is available through an EA-IND protocol held by the CDC that allows the use of stockpiled cidofovir for therapy of Orthopoxvirus (including MPXV) infections during an outbreak. Both brincidofovir and cidofovir inhibit poxvirus DNA replication by targeting viral DNA polymerase. Tecovirimat (also known as ST-246), developed by SIGA Technologies and licensed as TPOXX, was the first drug to get FDA approval for treating smallpox in adults and children, in 2018.[30] Tecovirimat interferes with the maturation and release of orthopoxviruses from infected cells by inhibiting the highly conserved p37 envelope-wrapping protein found in all orthopoxviruses. No randomized controlled data presently exist on tecovirimat efficacy in treating MPXV infections, but it proved effective in treating disease caused by orthopoxviruses in different animal models. Its favorable safety profile was confirmed in a placebo-controlled trial, with common side effects including nausea, vomiting, abdominal pain, and headache. No serious adverse events occurred, although one participant had to discontinue the drug as a result of electroencephalogram abnormalities.[31] The CDC holds an EA-IND protocol (also called "compassionate use") for use of stockpiled tecovirimat, available as a pill or an injection, to treat Mpox during an outbreak.

There remains a clear need for randomized controlled data on the efficacy of antivirals for the treatment of Mpox.[32] In September 2022, researchers at the Institut National de la Recherche Biomédicale in the DRC launched a 5-year, randomized, placebo-controlled clinical trial, PALM007. The primary objective is to compare the clinical efficacy, as assessed by time to lesion resolution, of tecovirimat and placebo in patients with Mpox. Secondary objectives include evaluations of virologic efficacy, as assessed by time to resolution of viremia, and clinical efficacy, as assessed by mortality, clinical severity, and duration of symptoms. The PALM007 trial builds on the research infrastructure and expertise of the PALM program (from Swahili: "pamoja tulinde maisha," meaning "together save lives"), which was initiated in 2018 as part of the emergency response to the 2018 Ebola outbreak in Eastern DRC. The PALM Ebola trial used an adaptative master protocol to show that both mAb114 and REGN-EB3 were superior to ZMapp in reducing mortality from Ebola[33] and demonstrated that scientifically and ethically sound clinical research can be conducted locally during disease outbreaks to help guide the outbreak response.[33] Master protocols can be used across outbreaks to compare therapeutics to standards of care, placebo, and active controls or in factorial designs.

As an example of leveraging the WHO master protocol, randomized trials of tecovirimat for nonhospitalized patients with Mpox presenting at sexual health clinics have been planned in Canada (PLATINUM-CAN), the United States (STOMP), and European Union (Epoxy-Trial). However, after a peak in August 2022, the number of Mpox cases in nonendemic countries declined steeply. The planned/ongoing trials might therefore face recruiting difficulties. Meanwhile, endemic countries in Africa remain heavily burdened by Mpox, and cases are expected to continue unless mass vaccination campaigns are implemented. Therefore, it is likely that efficacy data on the use of tecovirimat will primarily come from the PALM007 trial in the DRC.

Pending the results of the above trials, the WHO and professional bodies recommend tecovirimat for the treatment of serious cases of Mpox and the third-generation smallpox vaccine Imvanex for prophylaxis in all contact cases and among people at high risk of infection, including healthcare workers. Also, in the United States, the CDC holds an

expanded access protocol that allows for the use of Vaccinia immune globulin for the treatment of severe Orthopoxvirus (including MPXV) infections. Such treatments and vaccines need to immediately be made universally available and affordable using expanded access mechanisms for investigational new drugs or vaccines.

Recommended control measures in Mpox include 1) intensified surveillance and active case searches using standardized case definitions; 2) prompt sample collection (swabs of lesions, fluid samples, or crusts from active cases and serum for retrospective cases) for laboratory diagnosis and confirmation of cases; 3) isolation of suspected and confirmed cases; 4) strict adherence to infection control precautions, especially hand hygiene; 5) practices to avoid transmission by sexual or intimate contact, including strict hygiene measures among potential contacts, as spread can be due to any skin contact; 6) barrier nursing via the use of personal protective equipment; and 7) risk communication and social mobilization of the community regarding preventive measures. Furthermore, it is critical for public health institutions, local governments, and international stakeholders to ensure prompt coordination of structured responses to Mpox outbreaks. This might involve activation of existing epidemic preparedness or activation of an emergency operations center.[34] Furthermore, there is a need for strengthening national and international partnerships involving public health laboratories for the coordination of epidemiological surveillance including points of entry outbreak surveillance, case investigation, and contact tracing, as well as timely information sharing and risk communication for travel information guide updating and monitoring of animal and human populations using the "One Health" approach to detect outbreaks promptly before global spread.[35]

Moving forward, ongoing lessons learned from the recent Mpox outbreaks call for increased investment in research, capacity development, surveillance, and early detection via global, collaborative, and multidisciplinary research networks for neglected emerging and reemerging zoonotic pathogens in Africa and elsewhere. This approach is appropriate for three reasons. First, it will help to address humanitarian needs caused by the burden of disease in hotspots (e.g., Africa for Mpox). Second, because infectious diseases commonly cross borders, it is in the best interest of all—north, south, east, and west—to address infectious disease outbreaks early, whenever and wherever they emerge. Third, global networks are needed so that expertise and capacities can be quickly shared to speed up innovation and enable rapid responses during an outbreak, resulting in high-quality trials of novel diagnostics, therapeutics, and vaccines.[10] Political endorsement from individual countries and nationally owned financial commitment will be essential for long-term sustainability.

Ebola and Mpox were responsible for global outbreaks in 2014 and 2022, respectively, and both outbreaks made historically neglected tropical diseases highly visible, with headline news that attracted funding, international cooperation, and a global health response. However, in the case of Ebola, the momentum seemed to evaporate almost as soon as the threat to the Global North was gone. It is as yet unclear whether the same will happen with Mpox, as case burdens decrease in the Global North. We can break the cycle of neglect by maintaining support for diagnostics, therapeutics, vaccines, and research so that Mpox becomes the exception to the neglect rule. We call for the urgent establishment of best practices for future outbreaks. This should include establishment of stockpiles of key tools in endemic settings. Furthermore, there remains an unmet need to conduct a situational analysis of the true burden of MPXV infection around the world. Strengthened Mpox surveillance and diagnostics in endemic regions are urgently needed because this is the basis upon which targeted public response and critical studies can be leveraged. Finally, we commend the involvement of frontline researchers, communities, and relevant sites in Africa, where Mpox has long been endemic, for their contributions to the global research effort for new therapeutics and vaccines. To acknowledge these contributions and tackle global health inequities, any discoveries resulting from ongoing research efforts should be made widely available to local populations in countries endemic for Mpox and other outbreak diseases.

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Disclosure: We searched PubMed using medical subject headings (MeSHs). We focused on keywords and related variants to monkeypox (MeSH terms: MESH.EXACT["Monkeypox"] OR MESH.EXACT["Monkeypox virus"]). We also searched terms related to Variola virus, Vaccinia virus, Orthopoxvirus, and smallpox vaccine. We reviewed articles discussing the etiology, vaccination, and transmission of monkeypox virus in both humans and animals that were published in English up to November 2022. The authors were also recommended specific articles to review. The final reference list was generated based on the relevance of the articles to the scope of this viewpoint. The views and conclusions in this paper are those of the authors and do not necessarily represent the views of their institutions.

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