OVERVIEW OF MPOX ANTIVIRALS AND DIAGNOSTICS LANDSCAPE

This review has been commissioned by Unitaid in order to understand the main access barriers and the market situation of current medical countermeasures (in particular, therapeutics and diagnostics) to the management of mpox, to better understand potential roles and necessary interventions, if any, in the future.

This report is not indicative of an intention by Unitaid to support and/or fund investments in this area.

This is shared in the public domain hoping it can be useful information for others interested and/or working against this disease.

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EXECUTIVE SUMMARY

A new globalized outbreak of monkeypox (since 28 November 2022 denominated mpox by the World Health Organization, WHO) began in April 2022, expanding the presence of the virus beyond the countries and regions in which it is endemic, and spreading primarily through sexual routes of transmission that had not been identified or associated with other outbreaks. Mpox was declared a Public Health Emergency of International Concern (PHEIC) by the WHO Director-General on July 23, 2022.

This ongoing outbreak has been localized in communities of gay men and other men who have sex with men and transgender people, with additional cases in cis-gender women and children. As of 13 November 2022, 110 countries, territories or areas (per WHO classification) had reported cases, contributing to a global total of 79 411 laboratory confirmed cases and 50 deaths. At that time, 18 countries reported increases in cases, and 63 countries had not reported cases in the last 21 days. Cases in other countries were declining. While the overall trends in declining cases are encouraging, it is possible, if not likely, that many countries and communities that did not have endemic mpox prior to the start of the 2022 outbreak will join West and Central Africa–areas of historic endemicity–as endemic regions with the potential for intermittent outbreaks. The most recent outbreak, which saw high case rates in high-income countries, was characterized by a mobilization of testing, treatment and vaccine strategies that was a stark departure from the response to past and concurrent African outbreaks. Coming two years into the SARS CoV-2 pandemic, the mpox outbreak once again revealed stark global inequities in access to crucial medical countermeasures. This rapid landscape was designed to support continued action and coordination on the part of WHO, industry, funders, governments and communities to ensure reliable and equitable supplies of and global access to medical countermeasures for mpox virus.

This rapid landscape analysis is centered on the antiviral treatment tecovirimat and point-of-care diagnostic tools and does not explore the landscape of mpox vaccine access. It is designed to provide a starting point for discussions, further analysis and action on potential interventions needed to ensure that both testing and treatment can be made readily available for all populations in need.

As the treatment section describes, **significant, yet surmountable barriers to expanding access to tecovirimat** for mpox include:

- The present lack of clinical trial evidence for the efficacy of tecovirimat as treatment for mpox disease – noting that four clinical trials began in late 2022 and will start reporting results in 2023 and that WHO has published a protocol that can be used to design and conduct trials of tecovirimat for mpox in countries where the drug is not approved for that use)

- The heterogenous regulatory situation regarding the use of the drug for mpox disease (*e.g* it is approved only for smallpox in the U.S. and remains under an investigational new drug protocol for mpox, while it is approved for mpox in the European Union).

- Gaps in genomic surveillance and sequencing capacities within and between countries and regions make it difficult to monitor for tecovirimat resistance, which has been documented in rare instances in the current outbreak.

- Uncertainties with regard to commercial price, need and demand. SIGA, Inc., a US-based company that is the sole manufacturer of the medication, reports that it has only sold the drug to governments, with price pegged to the size of the order. The United States paid roughly USD$ 310 per course for its order of 1.7 million doses. Canada paid roughly USD$ 933 per course for its order of 15,325 courses in 2021. As of November 2022, SIGA donated 2500 courses of treatment to the WHO which has invited low- and middle-income countries to request doses free of charge. SIGA has also donated courses of the drug to countries in the Latin American region directly through its compassionate use program, reporting requests for tens or dozens of courses per country.

- As of November 2022, there is high level of uncertainty on demand size, with limited availability of data and evidence (for example, only a preliminary dosing regimen exists and the epidemiological situation is evolving in different geographies). Reliable models to estimate regional or global demand are not available and building them would require additional evidence on treatment regimens and further certainty on the patterns of outbreaks.

The information gathered in this high-level analysis regarding the access profile for tecovirimat indicates that:

- **If drug supply is determined to be a barrier to access, manufacturing of tecovirimat could be scaled expeditiously**. All production methods reviewed in the literature utilize common reactants, production steps, intermediaries, and purification methods. Consequently, the active pharmaceutical ingredient (API) market could easily meet global needs if these were to grow, while further analysis on timelines and volumes would be needed. Likewise, analysis of pricing levels, and linkage with volumes , is warranted.

- As SIGA Technologies, Inc. has already outsourced the manufacturing of oral tecovirimat to four contract manufacturing organizations, and a possibility of **tech transfer to additional manufacturers to scale production if needed should be explored as relevant.**

- The intellectual property (IP) portfolio for tecovirimat could enable a potential manufacturing-based expansion if needed, given the status of key patents for this product. **However, further analysis is needed for a comprehensive understanding of potential IP barriers** (potentially related to the method of use and polymorph patents) **to scaling tecovirimat production with additional manufacturers.**

As the diagnostics section of this landscape describes there are nearly a dozen commercially available rapid antigen diagnostics that indicate regulatory achievement. This information is drawn from the database of mpox diagnostics that is maintained by FIND and also includes antibody and molecular diagnostics. This landscape, including results of literature review to identify peer-reviewed and/or pre-print literature about mpox diagnostics, is

designed to complement that database, with a specific focus on point of care and near point of care diagnostics, which are valuable tools for detection and diagnosis in settings where lab-based PCR testing—the curent diagnostic gold standard for mpox—is in short supply or has long turnaround times.

Looking across all diagnostic categories, the landscape notes the need for, and ongoing work on, validating and establishing quality-assurance for mpox diagnostics. All of the rapid diagnostics that indicate regulatory approval cite Conformité Européenne (CE). CE marking on a product indicates that the manufacturer or importer of that product affirms its compliance with the relevant EU legislation and the product may be sold anywhere in the European Economic Area. CE marking is not equivalent to SRA authorization, review or approval. Steps that could lead to such authorization were underway as this report was finalized in late 2022 and are further described in the diagnostic section of the landscape, including the ongoing evaluations led by FIND.

The primary diagnostic method of mpox virus globally is swab-based laboratory reaction (PCR) testing. Stringent regulatory authorities have already examined data for and authorized the use of DNA polymerase chain reaction (PCR) kits. China's National Medical Products Administration (NMPA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) have authorized use of DNA PCR kits—two from the UK and one in China. The US Food and Drug Administration (FDA) has granted Emergency Use Authorization for three DNA PCR kits as of December 2022.[1] There has been limited information on comparative performance of PCR kits during the current mpox outbreak; here, as with rapid antigen tests, the gaps are being filled in. A WHO-supported evaluation of eleven commercially available PCR kits for the detection of DNA from mpox (clades I, IIa and IIb), other orthopox viruses and Variola virus[2].

The diagnostics landscape for mpox is, at present, centered on lesion-based sampling. The WHO recommended sample types are lesion exudate, roofs from more than one lesion, and lesion crusts; however PCR tests have detected mpox infection in anorectal swabs obtained during routine sexually transmitted infection screening of asymptomatic (lesion-free) individuals. It is not yet clear if and/or how often asymptomatic individuals shedding virus may pass on the virus; as data on this question is collected, the use of diagnostics to inform vaccination and treatment strategies during outbreaks will need to be revisited and possibly refined.

There is a clear need for a broader array of accurate, inexpensive point of care and near point of care diagnostics. At present, laboratory-confirmed mpox diagnostic capacity is largely based in high-income countries. While the WHO has distributed pre-designed PCR primer and probe test kits to LMICs without the laboratory capabilities to adapt published PCR primer and probe sequences, PCR testing infrastructure itself is limited in many LMICs. This limited infrastructure is often centralized in national laboratories or in additional urban areas, leading to slow test turnaround times, particularly in rural areas and, in all likelihood, under-counting of cases. There is therefore an urgent need to develop low-cost, accurate point of care diagnostics.

1 US Food and Drug Administration (2022). "Monkeypox Emergency Use Authorizations for Medical Devices." https://www.fda.gov/medical-devices/emergency-use-authorizations-medical-devices/monkeypox-emergency-use-authorizations-medical-devices?utm_medium=email&utm_source=govdelivery#molecular. Accessed: December 13, 2022.

2 Janine Michel, et al. "Evaluation of Eleven Commercially Available PCR Kits for the Detection of Monkeypox DNA." *MedRxiv.* October 19, 2022 https://www.medrxiv.org/content/10.1101/2022.10.14.22281096v1. Accessed 13 December 2022.

This landscape identifies opportunities to rationalize and shape the mpox diagnostics field, including:

- **Continued WHO action to build global capacity for laboratory-based diagnosis that is integrated within surveillance and epidemiological systems.** WHO is presently working with technical partners to validate available assays, the majority of which, as this review confirms, have limited validation data available. WHO is also supporting scale-up of testing by shipping samples to referral laboratories, procuring commercial kits and primer/probe and positive control material for use in low and middle income countries (LMICs) and sharing of testing materials.

- Following diagnostic validation, WHO emergency use listing for and/or pre-qualification of specific diagnostics could be considered in order to assist countries and other purchasers in identifying and making procurement decisions about commercially available tests. **The WHO's support of head-to-head evaluation of PCR kits provides valuable information; comparable information on rapid antigen tests, paired with assessment of cost and manufacturing parameters** that would impact scaling and commercialization will provide additional insights to inform decision making and and service delivery.

- **Exploration of diagnostic approaches to support routine, non-invasive screening, potentially as part of a multiplex assay.** At present mpox diagnosis requires a swab from a lesion and the test is conducted on the basis of symptoms and/or exposure reported by patients. Exploration of opportunities to incorporate mpox into standard point of care screening assays for sexually transmitted infection (STI) screening assays so that routine diagnosis for herpes simplex virus 2 (HSV-2), mpox and syphilis could be done with a single POC test. This is a priority that has been identified by the US government mpox coordinator as crucial to routinizing case detection in endemic contexts in the US; development of multiplex assays should not, however, be prioritized over the rapid development and evaluation of mpox tests, as the timelines for a multiplex assay may be longer.

- **Integration of PCR testing** for mpox using available platforms (Gene-Xpert), and guided by Diagnostic Network Optimization[3]. Even as rapid antigen diagnostic tests (Ag RDTs) and other tests are pursued, it will be important to develop rapid-integrated point of care PCR tests for mpox screening and monitoring especially amongst key populations (gay men and other men who have sex with men, transgender people, people with housing instability and living in congregate settings), and allow detection of infection and viral shedding in asymptomatic individuals.

The information gathered in this high-level analysis regarding diagnostics for mpox indicates that:

- In the context of the current mpox outbreak, **the pace at which rapid antigen tests entered the market outstripped global and national validation and regulatory approval**, with all rapid tests indicating regulatory achievement citing Conformite Europeenne, only

3 FIND, USAID, CDC, ASLM, IDC, BMGF. 2021. *Diagnostic Network Optimization: A Network Analytics Approach to Design Patient-Centred and Cost-Efficient Diagnostic Systems.* https://www.finddx.org/wp-content/uploads/2022/09/20220909_guide_to_DNO_FV_EN.pdf Accessed 13 December, 2022.

- **Diagnostics using loop-mediated isothermal amplification (LAMP) in development for mpox could be an alternative to gold-standard PCR testing.**

- **Available diagnostics may not be adequate to ongoing outbreak detection**– especially if asymptomatic transmission emerges as a factor.

Both the diagnostics and therapeutics landscapes identify areas requiring additional resources, coordination and actions to facilitate the availability and future deployment of medical countermeasures for management of mpox.

These include: estimations of potential need for therapeutics and diagnostics in different epidemiological scenarios in newly and historically endemic countries and regions to provide visibility of the potential ranges for the total need for production; visibility on prices including for LMICs; funding for a prioritized research agenda guided by the WHO R&D Blueprint group and addressing key areas identified in the WHO Strategic Preparedness, Readiness and Response Plan, including validation of existing diagnostics, research to improve understanding of viral kinetics, in order to guide decisions about where and when to sample, and studies of the effectiveness of tecovirimat alone and in combination with vaccines. Many of these issues have been identified by WHO and member states. This rapid landscape is only designed to provide additional detailed information to catalyze discussion, decision making and action.

INTRODUCTION

On 23 July, 2022, the WHO Director-General declared the escalating mpox outbreak a Public Health Emergency of International Concern (PHEIC). This declaration came roughly two months after the first reports of cases of mpox outside of previously endemic West and Central African regions. The vast majority of these cases were in gay men and other men who have sex with men and transgender individuals, with outbreak clusters in the United States and Europe reported in May 2022. By the time the PHEIC was declared, the outbreak was understood to be associated with sexual and/or skin-to-skin contact, resulting in lesions on the anus and genital areas. The routes of transmission and clinical presentation were atypical in comparison with prior outbreaks in the West and Central African general population. Diagnoses climbed steadily throughout June, July and August 2022, with the majority of cases in the United States, UK and Europe.

The availability of and information about mpox treatment and diagnostics has evolved rapidly over the course of the current outbreak. Access has been impacted by regulatory barriers, with lack of approval of tecovirimat for mpox in many countries, including the US, by data gaps from the safety and efficacy of tecovimirat for mpox, including for different clades-sub-types in different geographical regions, or validation data for available diagnostic tests. The ability to gather this information in a timely manner is further impacted by the epidemiology of the current outbreak. As of 13 November, 110 countries, territories or areas (per WHO classification) had reported cases, contributing to a global total of 79 411 laboratory confirmed cases and 50 deaths. At that time, 18 countries reported increases in cases, and 63 countries had not reported cases in the last 21 days. Cases in other countries were declining.

Yet there is still a need to gather, discuss and take decisions based on available information related to treatments and diagnostics. It is likely that many countries and communities that did not have endemic mpox prior to the start of the 2022 outbreak will experience some level of endemicity, with the potential for intermittent outbreaks; regions where the virus has long been endemic have little or no access to tecovirimat and highly limited access to laboratory-based diagnosis. Ensuring equitable access to tests and treatments over the long-term is essential for countries and communities where mpox is a recent development–and those where it has long been a threat.

This rapid landscape analysis, which is focused exclusively on the antiviral tecovirimat (Part I), and diagnostic tools (Part II), is designed as a resource for stakeholders seeking to ensure an equitable and sustainable response with a focus on low and middle-income countries. *In the treatment section, special emphasis is therefore placed on existing manufacturing and intellectual property status of tecovirimat, routes to removing access barriers, if and when they emerge, and an assessment of available information about drug price and compassionate use donation programs. In the diagnostic section, the focus is on summarizing (i) the array of diagnostics that have been registered in the FIND mpox diagnostic database and (ii) the available published peer-reviewed or pre-print validation data on the subset of these diagnostics for which the information is available. There are many tests available and only a few have validation data, a gap that WHO has also noted. This section identifies usability and performance considerations based on available data and underscores the need for additional research in the diagnostics space.*

This landscape analysis does not include programmatic recommendations or programmatic implications and builds on the work advanced in determining priorities and needs for R&D (including WHO R&D Blueprint), diagnosis mapping (FIND) and multiple other partners conducting R&D and programmatic activities.

This rapid landscape should serve as starting point for further and deeper review, as relevant, of the situation regarding access to optimal treatment and diagnosis of mpox virus, enabling reflections on potential interventions needed to secure an equitable access to these life-saving tools for LMICs, adjusted to evolving epidemiologic scenarios in the different geographies.

PART I: TECOVIRIMAT LANDSCAPE ANALYSIS

This analysis reviews the regulatory status and recommended use of tecovirimat globally, the evidence-base for tecovirimat use in mpox treatment, the ongoing research on tecovirimat and additional research needs, the state of tecovirimat supply and access globally, the potential for rapid scale-up of tecovirimat manufacturing, and global patent status for tecovirimat.

There are currently three antivirals approved by regulatory authorities for smallpox that may prove beneficial in patients infected with mpox virus: tecovirimat (brand name TPOXX), cidofovir (brand name Vistide), and brincidofovir (brand name Tembexa).[4] In one randomized clinical trial of another disease, patients who took brincidofovir for longer than the recommended duration had an elevated risk of mortality, and the drug label carries a warning about this risk, which is also a concern for cidofovir.[5,6] This review did not look in depth at the landscape for treatment modalities for patients with severe mpox who may require longer courses of treatment with oral tecovirimat, IV tecovirimat, IV cidofovir and IV vaccinia immuneglobulin or early research for novel therapeutics. In one study, the majority of individuals experiencing severe mpox requiring hospitalization were people living with HIV who were severely immunocompromised[7]. This landscape focused on treatment for the clinical symptoms experienced by the majority of people with mpox. Looking at the guidance, treatment and research needs for mpox as an HIV-related opportunistic infection is an important area of additional work.

1.1 REGULATORY STATUS AND RECOMMENDED USE OF TECOVIRIMAT

One of the challenges and opportunities in terms of medical countermeasures for mpox is the existence of an effective antiviral, that, on the one hand, is approved for both smallpox and mpox in the EU and UK, and for smallpox in the United States, where it is available for mpox only under an Expanded Access Investigational New Drug protocol.

Tecovirimat was developed by the US-based company SIGA Technologies, Inc. with significant funding from the U.S. government.[8] The drug prevents cellular transmission of mpox virus by inhibiting the function of a major envelope protein required for extracellular viral production.[9] It can be taken orally or intravenously. It was approved by the US Food and Drug Administration (FDA) in 2018 for treatment of smallpox. Since May 2022, it has been available via an expanded access investigational new drug (EA-IND) protocol through

4 US Centers for Disease Control and Prevention. "Monkeypox: Treatment Information for Healthcare Professionals." Last updated October 3, 2022. https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html Accessed November 29, 2022.

5 *See* FDA. (September 2000). Vistide [package insert]. Gilead Sciences, Inc. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/020638s003lbl.pdf

6 *See* FDA. (June 2021). Tembexa [package insert]. Chimerix, Inc. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214460s000,214461s000lbl.pdf

7 Miller MJ, Cash-Goldwasser S, Marx GE, et al. 2022. "Severe Monkeypox in Hospitalized Patients — United States, August 10–October 10, 2022." *MMWR Morb Mortal Wkly Rep* 2022;71:1412–1417. DOI: http://dx.doi.org/10.15585/mmwr.mm7144e1. Accessed 13 December, 2022.

8 Nolen, Stephanie. (2022, September 12)."Monkeypox Shots, Treatments and Tests Are Unavailable in Much of the World." *The New York Times*. https://www.nytimes.com/2022/09/12/health/monkeypox-vaccines-treatments-equity.html. Accessed November 29, 2022.

9 *See* FDA. (2018) New Drug Application (NDA) Approval Letter for NDA 208627. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/208627Orig1s000ltr.PDF

the U.S. Centers for Disease Control for patients with severe mpox disease.[10,11] In contrast, the European Medicines Agency (EMA) approved tecovirimat in 2021 with indications for both smallpox and mpox.[12]. The WHO has not included this medicine in the Emergency Use Assessment and Listing (EUAL) procedure, while the MEURI Ethical Framework (updated by WHO in 2022) provides guidance for use of unproven clinical interventions outside clinical trials during public health emergencies, including for tecovirimat (see WHO, Emergency use of unproven clinical interventions outside clinical trials: ethical considerations, April 2022).

1.2 EFFICACY DATA AND GAPS

The FDA and EMA approvals of tecovirimat for use without restriction for smallpox (US) and smallpox and mpox (EMA) were based on a dossier that included efficacy data from animal studies (using mpox virus in primates and rabbitpox virus in rabbits) and phase III safety data in healthy human volunteers.[13,14]

Observational data from the US CDC has been reported for tecovirimat including, as of August 2022, intake and outcome forms from 549 and 369 patients, that found low rates (3.5 percent) of adverse events, with all but one of these events (psychiatric hospitalization) classified as non-serious. This analysis reported a median time from initiation to resolution of symptoms of three days (based on subjective reporting) with no difference between people living with HIV (PLHIV) and those who were HIV negative[15]. Information on mpox vaccine and treatment effectiveness for PLHIV is highly relevant in the current outbreak, as PLHIV comprise roughly 40 percent of all individuals with known HIV status diagnosed since May 2022. PLHIV who are not virologically suppressed or who have HIV-related immunosuppression may be at a higher risk of severe disease, more likely to be hospitalized, and/or have more prolonged symptoms[16,17]. The overlap of severe mpox disease and HIV-related immunosuppression reinforces racial and economic disparities in access to care and health outcomes–in one United States cohort of hospitalized individuals co-infected with mpox and HIV, nearly 70 percent were Black gay men with AIDS[18].

Additional evidence is needed to define clinical efficacy of tecovirimat in humans infected with mpox virus who are living with other underlying conditions, particularly HIV, and to explore it as a possible pre-exposure prophylaxis (PrEP) and/or post-exposure prophylaxis (PEP) modality. There is research underway to address some, though not all, of these questions. The current ongoing and planned trials are described in the next section, followed by a brief overview of remaining research gaps.

10 *Ibid*
11 CDC (2022). Guidance for Tecovirimat Use. Updated September 15, 2022. Available at: https://www.cdc.gov/poxvirus/monkeypox/clinicians/Tecovirimat.html. Accessed November 29, 2022.
12 SIGA. (2022). SIGA Technologies Receives Approval from the European Medicines Agency for Tecovirimat. Available at: https://investor.siga.com/news-releases/news-release-details/siga-technologies-receives-approval-european-medicines-agency.
13 *See* Center for Drug Evaluation and Research. (2018) Clinical review for NDA 208627. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208627Orig1s000MedR.pdf.
14 EMA (2022). Tecovirimat SIGA. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/tecovirimat-siga Accessed November 29, 2022.
15 O'Laughlin K, Tobolowsky FA, Elmor R, et al. (2022). Clinical Use of Tecovirimat (Tpoxx) for Treatment of Monkeypox Under an Investigational New Drug Protocol — United States, May–August 2022. MMWR Morb Mortal Wkly Rep 2022;71:1190–1195. DOI: http://dx.doi.org/10.15585/mmwr.mm7137e1. Accessed November 29, 2022.
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1.3 CURRENT RESEARCH AND RESEARCH GAPS FOR TECOVIRIMAT

Ongoing studies

Efficacy data for tecovirimat in humans is currently limited to case reports and data from observational studies from countries, primarily the US, United Kingdom (UK), European Union (EU) and Nigeria, which have used tecovirimat in the context of the current outbreak. Case reports have found that tecovirimat is "well tolerated and improves symptoms."[19] However, these data might be subjected to bias, lack a control group and do not provide insights into use of tecovirimat as PrEP and/or PEP or in conjunction with vaccines. There are trials underway that can provide insights into some, though not all, of these questions.

1. **Study of Tecovirimat for Human Monkeypox Virus (STOMP), conducted by the AIDS Clinical Trials Group (ACTG)[20]**

Planned sample size: 530
Location: 80 sites across the United States
Design: Randomized (2:1), double-blind, placebo-controlled
Inclusion criteria: Adults and children with mpox
Outcomes: Primary outcome is time to clinical resolution; secondary outcomes include pain and levels of mpox virus in various compartments (e.g., semen, blood, skin lesions)
Estimated completion date: September 30, 2023
Funder/Partners: U.S. National Institute of Allergy and Infectious Diseases (NIAID)

2. **The Placebo-controlled randomized trial of tecovirimat in non-hospitalised monkeypox patients (PLATINUM)[21]**

Planned sample size: 500
Location: United Kingdom
Design: Randomized (1:1), double-blind, placebo-controlled
Inclusion criteria: Adults and children with laboratory-confirmed mpox
Outcomes: Primary outcome is time to resolution of active lesions; secondary outcomes include time to negative cultures in throat and lesion swabs and time to complete resolution.
Estimated completion date: NA
Funder/Partners: U.K. National Institute for Health and Care Research, Oxford University.

3. **Tecovirimat in Non-hospitalized Patients With Monkeypox (PLATINUM-CAN)[22]**

Planned sample size: 120
Location: Canada
Design: Randomized (1:1), double-blind, placebo-controlled
Inclusion Criteria: Adults (18 years and older) with laboratory confirmed or presumptive mpox

19 Desai, A., Thompson, G, & Neumeister, S. (2022) Compassionate Use of Tecovirimat for the Treatment of Monkeypox Infection JAMA 328(13):1348-1350. doi:10.1001/jama.2022.15336. Accessed Sept. 27, 2022.
20 Study of Tecovirimat for Human Monkeypox Virus (STOMP). ClinicalTrials.gov Identifier: NCT05534984. Last updated November 14, 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT05534984?term=tecovirimat&draw=2&rank=10. Accessed November 29, 2022.
21 University of Oxford. (2022, August 24). "Oxford University launch new clinical trial to test a treatment for monkeypox." Available at: https://www.ox.ac.uk/news/2022-08-24-oxford-university-launch-new-clinical-trial-test-treatment-monkeypox. Accessed November 29, 2022.
22 Tecovirimat in Non-hospitalized Patients With Monkeypox (PLATINUM-CAN). ClinicalTrials.gov identifier: NCT05534165. Last updated September 9, 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT05534165?term=UNITY&cond=monkeypox&draw=2&rank=2. Accessed November 29, 2022.

Outcomes: Primary outcome is time to resolution of active lesions; secondary outcomes include time to negative cultures in throat and lesion swabs and time to complete resolution.
Estimated completion date: February 2023
Funder/Partners: McGill University Health Centre/Research Institute of the McGill University Health Centre, University Health Network, Toronto, Unity Health Toronto, University of British Columbia, CIHR Canadian HIV Trials Network

4. Tecovirimat for Treatment of Monkeypox Virus, conducted by the Institut National de Recherche Biomédicale of the Democratic Republic of the Congo (D.R.C.) (PALM 007)[23]

Planned sample size: 450
Location: Tunda, D.R.C. and Kole, D.R.C.
Design: Randomized (1:1), double-blind, placebo-controlled
Inclusion Criteria: Adults including pregnant and breastfeeding women and children weighing <3 kg with mpox
Outcomes: Primary outcome is time to lesion resolution; secondary outcomes include mortality and time to two consecutives negative mpox virus PCR test results
Estimated completion date: September 2024
Funder/Partners: U.S. NIAID, Institut National de Recherche Biomédicale. Kinshasa, République Démocratique du Congo

5. Assessment of the Efficacy and Safety of Tecovimirat in Patients with Monkeypox Virus Disease[24] (UNITY)

Planned sample size: 1,152
Location: Brazil and other countries in Latin America, Switzerland (n.b. to be extended to African sites)
Design: Randomized, double-blind, placebo-controlled
Inclusion criteria: 14 years or older with at least one visible lesion
Outcomes: Primary outcome is time to lesion resolution; secondary outcomes include all-cause mortality, unplanned hospital admission, viral clearance, adverse events.
Estimated Study Completion Gap: January 2025
Funder/Partners: Oswaldo Cruz Foundation (Brazil), Agence nationale de recherches sur le sida et les hépatites virales (ANRS, France) Emerging Infectious Diseases Additional co-sponsoring with other Latin America countries ongoing) in an innovative governance model.

6. Tecovirimat (ST-246) Treatment for Orthopox Virus Exposure[25]

Planned sample size: N/A
Location: Global US Department of Defense
Design: Expanded access
Inclusion criteria: US Department of Defense personnel and dependents of all ages (who are not breastfeeding) who have been exposed to or contracted mpox

23 Tecovirimat for Treatment of Monkeypox Virus. ClinicalTrials.gov identifier: NCT05559099. Last updated October 27, 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT05559099?term=tecovirimat&draw=2&rank=1. Accessed November 29, 2022.
24 Assessment of the Efficacy and Safety of Tecovirimat in Patients with Monkeypox. ClinicalTrials.gov identifier: NCT05597735. Last updated November 1, 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT05597735?term=UNITY&cond=monkeypox&draw=2&rank=1. Accessed November 29, 2022.
25 Tecovirimat (ST-246) Treatment for Orthopox Virus Exposure. ClinicalTrials.gov identifier: NCT02080767. Last updated July 25, 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT02080767?cond=Monkeypox&draw=2&rank=18. Accessed November 29, 2022.

Outcomes: Participants will be followed for thirty days after last dose, with information collected on symptoms, time to resolution, development of infection (for individuals taking tecovimirat as pre-exposure prophylaxis after exposure)

Research Gaps

The WHO R&D Blueprint group has held two consultations on trial designs and research priorities for mpox in the context of the current outbreak. No final reports from these consultations were available at the time of publication, however the Blueprint Group has published the "Core Protocol," for an adaptive multiregional international global randomized, placebo-controlled trial to evaluate the safety and efficacy of drugs for the treatment of human mpox (Phase 3)[26]. This protocol encourages collection of data on HIV status, which will provide additional insights into clinical outcomes and therapeutic efficacy in this key population. Additional areas suggested by the current outbreak and the pipeline of planned and existing trials include:

1) Research gap: efficacy of tecovirimat when used as post-exposure prophylaxis (PEP) and/or pre-exposure prophylaxis (PrEP)

Tecovirimat has demonstrated potent post-exposure protective or prophylactic activity in numerous animal studies in which animals were challenged with orthopoxvirus infection.[27] Just one of the ongoing trials (#6 in the preceding list) is gathering data on tecovirimat as PEP, including in vaccinated and unvaccinated individuals. Additional information is needed on the medication as PEP and PrEP in vaccinated and unvaccinated individuals. Although vaccines are available, these prophylactic uses of tecovirimat may be especially important in the present context of limited mpox vaccine supply globally, for people at high risk of severe disease (i.e. PLHIV who are immunosuppressed, children, pregnant women and other pregnant people) and if current emerging evidence of potential transmission occurring in the pre-symptomatic phase is confirmed.

2) Research gap: frequency of and contributing factors to tecovirimat-resistant mpox virus is needed

Gaps in genomic surveillance and sequencing capacities within and between countries and regions make it difficult to monitor for tecovirimat resistance, which has been documented in rare instances in the current outbreak. Mpox virus may be able to easily evolve to become resistant to tecovirimat. Just one amino acid change in the viral drug target has been shown to reduce tecovirimat activity *in vitro*.[28] Current planned and ongoing trials will provide limited insights into the risk of resistance as currently designed. In the STOMP trial, only 100 patients will be deeply sequenced. Sequencing all 530 participants in this study and exploring the possibility of sequencing samples from other studies would provide much-needed additional information.

26 WHO. (2022, July 24). "CORE PROTOCOL - An international adaptive multi-country randomized,placebo-controlled, double-blinded trial of the safety and efficacy of treatments for patients with monkeypox virus disease." Available at: https://www.who.int/publications/m/item/core-protocol---an-international-adaptive-multi-country-randomized-placebo-controlled--double-blinded-trial-of-the-safety-and-efficacy-of-treatments-for-patients-with-monkeypox-virus-disease, Accessed November 29, 2022

27 Smith et al. (2011, August 8). "Effective Antiviral Treatment of Systemic Orthopox Disease: ST-246 Treatment of Prairie Dogs Infected with Monkeypox Virus," Journal of Virology, Vol 85, no 17. https://journals.asm.org/doi/full/10.1128/JVI.02173-10 Accessed November 29, 2022. This paper describes seven studies that have evaluated tecovirimat's post-exposure protective or prophylactic efficacy in various animal models, including non-human primates.

28 The American Medical Association. (2022, September). "What Physicians Neet to Know about Tecovirimat 'TPOXX' for Treatment of Monkeypox." Webinar. Available at: https://www.ama-assn.org/about/events/what-physicians-need-know-about-tecovirimat-tpoxx-treatment-monkeypox. Accessed November 29, 2022.

3) Research gap: duration of treatment.

For example, CDC has reported on immunosuppressed patients having received treatments exceeding a duration of 3 months (notably immunosuppressed PLHIV).[29]

1.4 GLOBAL TECOVIRIMAT ACCESS LANDSCAPE

Affordability

SIGA, Inc., a US-based company that is the sole manufacturer of the medication, reports that it has only sold the drug to governments, with price pegged to the size of the order. The price for United States is roughly USD$ 310 per course for its order of 1.7 million doses. For Canada paid roughly USD$ 933 per course for its order of 15,325 doses. As of November 2022, SIGA donated 2500 courses of treatment to the WHO which has invited LMICs to request doses free of charge, under the MEURI protocol (see WHO, Emergency use of unproven clinical interventions outside clinical trials: ethical considerations, April 2022).

SIGA has also donated courses of the drug to countries in the Latin American region directly through its compassionate use program, reporting requests for tens or dozens of courses per country. SIGA Technologies, Inc. has publicly stated they are willing to scale manufacturing to serve LMIC markets; in its interview for this landscape analysis, the company also indicated its willingness to contribute a license to the Medicines Patent Pool. It has not stated an LMIC price.[30] No analysis of Cost of Goods (or cost of production) is yet available to estimate potential cost if generic production were to be supported.

Supply

As part of this landscape, SIGA was queried about its manufacturing capacity and reports capacity to manufacture 500,000 courses per year from a single US-based supply chain, with limited barriers to further scaling up manufacturing if warranted.

Demand

Demand for tecovirimat has grown in the context of the current outbreak, as evidenced by the orders by 12 international buyers announced on 26 September 2022[31] . Even with the compassionate use donations from SIGA direct to countries and to WHO, the majority of individuals with mpox accessing tecovirimat reside in the U.S. and Europe, where the drug has been part of national responses mobilized to the recent outbreak. Low demand in LMICs may be influenced by a combination of factors, including lack of diagnostics and underreporting including in endemic countries, relative non-severity of mpox disease in terms of rates of hospitalization and death, declining case rates, competing health priorities and lack of funding in addition to potential barriers for access, and unclarity on availability/ affordability for LMICs.

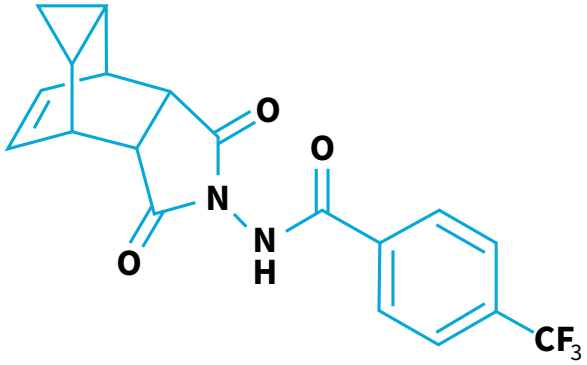
29 Morbidity and Mortality Weekly Report (MMWR) , October 26, 2022

30 Nolen, Stephanie. (2022, September 12).“Monkeypox Shots, Treatments and Tests Are Unavailable in Much of the World.” *The New York Times*. https://www.nytimes.com/2022/09/12/health/monkeypox-vaccines-treatments-equity.html. Accessed November 29, 2022.

31 SIGA. (2022, September 26). “SIGA Announces Approximately $16 Million of International Procurement Orders Received in August and Early September for Oral TPOXX (Tecovirimat).” Available at: https://investor.siga.com/news-releases/news-release-details/siga-announces-approximately-16-million-international. Accessed November 29, 2022.

1.5 TECOVIRIMAT MANUFACTURING SCALE-UP POTENTIAL

FIGURE 1. Molecular structure of tecovirimat



If drug supply is determined to be a barrier to access, a barrier to access "should potential demand outweight supply, manufacturing of tecovirimat can be scaled expeditiously both by SIGA Technologies and contract manufacturing organizations (CMO); other manufacturers could also develop it given the low manufacturing complexity and wide availability of chemicals needed for its synthesis.

Tecovirimat is achiral, meaning it does not have a mirror image molecule (enantiomer). This is significant, as enantiomers can often complicate the production of an active pharmaceutical ingredient (API). Furthermore, there are multiple routes to tecovirimat synthesis, all beginning with cycloheptatriene as a precursor molecule. Cycloheptatriene is a commonly synthesized organic compound, widely produced in the commercial market. Accessing cycloheptatriene would not be a barrier to scaling up manufacturing of tecovirimat, if demand increases.

This review analyzed methods of producing tecovirimat API available in the peer-reviewed literature. All methods reviewed utilize common reactants, production steps, intermediaries, and purification methods. [32]

For the manufacturing of oral tecovirimat, SIGA Technologies, Inc. uses four US-based contract manufacturing organizations (CMOs): W.R. Grace and Company (for bulk API); Powdersize (for micronizing API); Catalent Pharma Solutions LLC (for putting bulk API into capsules), and Packaging Coordinators, LLC (for packaging and labeling). SIGA has indicated willingness to expand production. Producing under the control of the originator could be faster, a consideration that could become relevant if additional supply is needed.

32 David L. Hughes. (2019, June 21). "Review of Patent Literature: synthesis and Final Forms of Antiviral Drugs Tecovirimat and Baloxavir Marboxil." Organic Process Research & Development, *23*, (7). DOI: https://doi.org/10.1021/acs.oprd.9b00144. Accessed November 29, 2022.

1.6 PATENT LANDSCAPE OF TECOVIRIMAT

Methods

This patent landscape utilized the U.S. FDA Orange Book, Google Patent, and the databases of the European Patent Office database, Indian Patent Office, and Mexican Patent Office. The landscape also utilized the World Intellectual Property Organization (WIPO) patentscape to search the molecular structure of tecovirimat to find any Patent Cooperation Treaty (PCT) filings that disclose the molecular structure of tecovirimat. This landscape does not cover the IV formulation of this drug, as its use is minimal for mpox. As this is a rapid patent landscape, it should not be treated as an authoritative analysis.

Results

Patent 1 is a method of use patent alleging to protect the use of tecovirimat and related compounds in treating or preventing an orthopoxvirus infection in a living organism. In addition to the United States patent being filed in 2004 (USPTO patent number US7737168B2), a PCT filing was made in 2007 and published by WIPO on 3 July 2008 (WIPO International Publication Number WO 2008/079159 A3).

No other patent could be identified that has been granted by any other patent offices. However, a European patent application was filed in 2007 that was later withdrawn, as well as a Canadian patent application in 2007 that was withdrawn. Following a patent term extension by the U.S. patent office of 1,049 days, the expiration date of Patent 1 is listed in the Orange Book as 4 September 2031.

US7737168B2 is the national phase/equivalent of PCT/US2004/019552 filed on 18.06.2004 and published as "https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2004112718&_fid=US41364013" WO2004112718 on 29.12.2004. The international patent application discloses tecovirmat compound and its analogues (generic Markush structure as well as specific compounds) as well as their use to treat or prevent an orthopoxvirus infection is a living organism. In addition to the US, equivalents were filed and granted in Australia, Canada, Europe (European Patent Office EP1638938) and Japan. The expected twenty years expiry date is 18/06/2024. Following a patent term extension by the U.S. patent office of 1,585 days (in addition to a patent term adjustment of 1049 days) the expiration date of Patent 1 is listed in the Orange Book as 4 September 2031. Patent term of few European countries has also been extended until 2029 (e.g. in the Netherlands, Sweden). Term extensions are pending in France, Germany and Spain.

Patent 2 is a formulation patent alleging to protect the formulation of tecovirimat or related compounds with commonly used pharmaceutical formulating agents for the oral drug. Specific formulations of a tecovirimat-containing oral drug product are claimed within the patent. The patent contains a Bayh-Dole march-in provision indicating the U.S. government has certain rights in the invention. A PCT filing was published by WIPO on 30 October 2008 (WIPO International Publication Number WO 2008/130348 A1). In addition to the U.S. and WIPO filings, from this patent family, two Australian patents were granted (AU2007351866 and AU2012268859) three Canadian patents were granted (CIPO patent numbers 2866037; 2685153; 2966466), four Israeli patents were granted (IL201736, IL242665, IL242666, IL269370), two Mexican patents were granted (MX patent numbers 348481; 363189). In addition, patent applications were filed in Europe but withdrawn, and filed and rejected in Japan and China. (divisional applications are pending in Australia and Mexico). The twenty years expected expiry date of these patents is 23.04.2027. Following a patent term extension by the U.S. patent office of 1,130 days, the expiration date of Patent 2

(US8039504B2) is listed in the Orange Book as 23 July December 2027 (the effective filing date of this patent was in 2004).

Patent 3 is a compound and drug product patent allegedly protecting the use of tecovirimat or other related compounds in a pharmaceutical composition. The patent contains a Bayh-Dole march-in provision indicating the U.S. government has certain rights in the invention. A PCT filing was published by WIPO on (WIPO International Publication Number WO 2008/079159 A3). Patent applications were filed in Canada (CIPO publication number CA268519A1), however the Canadian application was withdrawn in 2013. Patent 3 was also filed in Europe (publication numbers EP2192901A2; 2192901A4), but the applications were withdrawn in 2013. Country-specific searches were performed at the European patent office, the Canadian patent office, and the Indian patent office, and no related patents were found. Further investigation is needed to see whether there is patent protection in countries other than the United States against the core compound. The expiration date of Patent 3 is listed in the Orange Book as 18 June 2024.

Patent 4 is a method of use patent alleging to protect the use of tecovirimat and related compounds in treating or preventing an orthopoxvirus infection in a living organism. The patent contains a Bayh-Dole march-in provision indicating the U.S. government has certain rights in the invention. A United States patent was filed in 2011 (USPTO patent number US8530509B2). No other patent applications to other patent offices outside the United States were found. Following a patent term extension by the U.S. patent office of 77 days, the expiration date of Patent 4 is listed in the Orange Book as 18 June 2024.

Patent 5 is a method of use patent alleging to protect the use of tecovirimat and related compounds in treating or preventing an orthopoxvirus infection in a living organism. The patent contains a Bayh-Dole march-in provision indicating the U.S. government has certain rights in the invention. A United States patent was filed in 2013 (USPTO patent number US8802714B2). We could not identify any other patent applications to other patent offices outside the United States. The expiration date of Patent 5 is listed in the Orange Book as 18 June 2024.

Patent 6 is a polymorph patent claiming a polymorph as well as a pharmaceutical composition containing that polymorph formulated for oral administration as well as a method for producing that polymorph. The patent contains a Bayh-Dole march-in provision indicating the U.S. government has certain rights in the invention. A United States patent was filed in 2011 (USPTO patent number US9339466B2). A PCT filing was published by WIPO on 29 September 2011 (WIPO International Publication Number WO 2011/119698 A1). Patents from this family have also been granted by ARIPO (the African Regional Industrial Property Organization), OAPI (Organisation Africaine de la Propriété Intellectuelle), the EPO as well as in Brazil, Canada, China, , Israel, Japan, Mexico, Russia, South Africa, and Australia. In india, a patent application is pending and is under pre-grant opposition. Additional polymorph patents claiming additional, distinct polymorphs have also been filed and granted. These may be blocking patents. The expiration date of Patent 6 is listed in the Orange Book as 23 March 2031, the expected expiry date of other family members.

This patent family covers tecovirimat polymorphic Form I, the active ingredient which according to "https://www.ema.europa.eu/en/documents/assessment-report/tecovirimat-siga-epar-public-assessment-report_en.pdf" EMA assessment report (https://www.ema.europa.eu/en/documents/assessment-report/tecovirimat-siga-epar-public-assessment-

report_en.pdf) is “the most thermodynamically stable form of tecovirimat under common storage and handling conditions, and hence was chosen for commercial development(see pages 12-13).

Patent 7 . Three US patents have been listed in the orange book with respect to TPOXX solution 200MG/20ML (10MG/ML) US9233097, US9907859 and US10576165 with the expiry date 2 August 2031. The claims of the corresponding PCT, filed on 02.08.2011 and published as WO2012018810 on 9 February 2012 cover tecovirimat liquid pharmaceutical compositions comprising cyclodextrin. Equivalent patents have also been granted in Australia, Brazil, by the EPO, Israel, Japan, Korea, Mexico, south Africa and pending in Argentina, Canada, China, India and Singapore

TABLE 1. Patent families for tecovirimat by groups (as categorized by MPP)

	Description	Patent publication #	Expected date of expiry in LMICs	Source	Notes
Patent 1 (& 3-5)	Tecovirimat and analogues and their use to treat or prevent orthopoxvirus infections and compositions	WO2004112718	18.06.2024	US7737168 US8124643 US8530509 US8802714 US8039504 capsule Solution	US7737168 05/03/2027 + PTE 09/04/2031 U-2346 08/09/2018 US8124643 06/18/2024 DS DP08/09/2018 US8530509 06/18/2024 DP 08/09/2018 US8802714 06/18/2024 U-2346 08/09/2018
Patent 2	Tecovirimat and analogues compositions (water-insoluble diluent, …)	WO2008130348	23.04.2027	US8039504 capsule Solution	US8039504 07/23/2027 DP 08/09/2018 (CIP OF WO2004112718 however filed the same date as PCT WO2008130348 with same subject matter)
Patent 6	Polymorphic Forms of ST-246 and Methods of Preparation	WO2011119698	23.03.2031	US9339466 capsule	US9339466 03/23/2031 DS DP 08/09/2018 AP, AR (N), AU, BR, CA, CL (N), CN, HK, IL, IN, JP, KR (N), MX (G), NZ, PE (N), SG,
Patent 7	Tecovirimat liquid formulations (with cyclodextrin)	WO2012018810	08.02.2031	US9233097 US9907859 US10576165 Solution	IN305/KOLNP/2013

The patent information in low- and middle-income countries for tecovirimat is now available on MedsPaL (www.medspal.org) the Medicines Patents and Licenses Database since 14 December 2022.

Discussion

The findings of this rapid patent landscape suggest that the intellectual property portfolio for tecovirimat may be more surmountable than for many other novel small molecule medicines. SIGA’s intellectual property portfolio for tecovirimat is unusual in that the core compound patent, Patent 3, does not have an international filing, and is only filed in the United States. However, method of use patents and polymorph patents are widely filed, which may provide a barrier to manufacturers producing tecovirimat without a license. The polymorph patent, Patent 6, is the most extensively filed patent, and its patent family may contain blocking patents. **Further analysis is needed for a comprehensive understanding of potential IP barriers to scaling tecovirimat production by additional manufacturers continued discussions with SIGA have indicated “that they are exploring options for broader access, including voluntary licensing through the Medicines Patent Pool.”**

1.7 CONCLUSION

As the treatment section describes, **significant, yet surmountable barriers to expanding access to tecovirimat** for mpox include:

- The present lack of clinical trial evidence for the efficacy of tecovirimat as treatment for mpox disease – noting that four clinical trials began in late 2022 and will start reporting results in 2023 and that WHO has published a protocol that can be used to design and conduct trials of tecovirimat for mpox in countries where the drug is not approved for that use)

- The heterogenous regulatory situation regarding the use of the drug for mpox disease (*e.g,.* it is approved only for smallpox in the U.S. and remains under an investigational new drug protocol for mpox, while it is approved for mpox in the European Union)

- Gaps in genomic surveillance and sequencing capacities within and between countries and regions make it difficult to monitor for tecovirimat resistance, which has been documented in rare instances in the current outbreak.

- Uncertainties with regard to commercial price, need and demand. SIGA, Inc., a US-based company that is the sole manufacturer of the medication, reports that it has only sold the drug to governments, with price pegged to the size of the order. The United States paid roughly USD$ 310 per course for its order of 1.7 million doses. Canada paid roughly USD$ 933 per course for its order of 15,325 courses in 2021. As of November 2022, SIGA donated 2500 courses of treatment to the WHO which has invited LMICs to request doses free of charge. SIGA has also donated courses of the drug to countries in the Latin American region directly through its compassionate use program, reporting requests for tens or dozens of courses per country.

- At present, the demand for the medication is not reported by WHO or the company to be outstripping supply of free donated drug. Quantification of current demand and projected need in different scenarios of endemicity and occasional outbreaks could be beneficial as part of a strategy for meeting long-term needs–perhaps via a stockpile held at and dispensed by UNICEF or a non-governmental organization (NGO) distribution partner.

The information gathered in this high-level analysis regarding the access profile for this tecovirimat indicates that:

- **If drug supply is determined to be a barrier to access, manufacturing of tecovirimat could be scaled expeditiously**. All production methods reviewed in the literature utilize common reactants, production steps, intermediaries, and purification methods. Consequently, the active pharmaceutical ingredient (API) market could easily meet global needs if these were to grow.

- As SIGA Technologies, Inc. has already outsourced the manufacturing of oral tecovirimat to four contract manufacturing organizations, and a possibility of **tech transfer to additional manufacturers to scale production if needed should be explored as relevant.**

- The intellectual property (IP) portfolio for tecovirimat could enable a potential manufacturing-based expansion if needed, given the status of key patents for this product. **However, further analysis is needed for a comprehensive understanding of potential IP barriers** (potentially related to the method of use and polymorph patents) **to scaling tecovirimat production with additional manufacturers, as well as SIGA's approach regarding the access and licensing plans for tecovirimat.**

PART II: DIAGNOSTICS LANDSCAPE ANALYSIS

Rapid, accessible, and highly sensitive diagnostic technologies are essential to a comprehensive mpox virus epidemic control strategy. At present, there are significant gaps in the diagnostics landscape that will slow down rapid effective responses to new outbreaks and ongoing endemic transmission. These include lack of validation data for a range of commercially available rapid antigen tests and reliance on swab-based PCR testing for confirmatory diagnosis. Complex and/or painful specimen collection requirements coupled with a testing approach that is in short supply in many geographies put ongoing routine surveillance and accurate diagnosis out of reach in many settings.

Table II summarizes the current landscape of approved and late-stage diagnostics included in the database of mpox diagnostics that is maintained by FIND.[33] That database also contains diagnostics in earlier stages of development and those approved for research use only and is updated regularly. This landscape is designed to complement the database with a closer look at the limited validation, performance and sensitivity data available on molecular and rapid antigen tests.

TABLE II. The Mpox Diagnostics Landscape of Late-Stage and Approved Diagnostics in FIND Mpox Test Directory as of November 2022

	N. of tests in FIND Database (as of 30 November 2022)	N. of tests at validation stage	N. of tests in late-stage development (fully functional prototype)	N. of tests with use authorized by national regulatory authority incldluing US FDA, MHRA UK, China NMPA[34]	N. of tests with CE marking
Antibody	12	0	0	0	5
Antigen	14	0	1	0	11
DNA	90	8	2	4	56
RNA + DNA	2	0	0	0	0

2.1 OVERVIEW OF EXISTING DIAGNOSTIC APPROACHES AND REGULATORY LANDSCAPE FOR MPOX VIRUS DIAGNOSTICS

The WHO new mpox Strategic Preparedness, Readiness and Response Plan (published October 2022)[35] highlights the potential of rapid, point-of-care diagnostics to serve as valuable tools for early case detection and population surveillance of mpox virus. According

33 FIND MPX Test Directory (2022). Available at: https://www.finddx.org/mpx-test-directory/.

34 The totals reported on the FIND Database for regulatory authorization by SRAs do not reflect US Emergency Use Authorizations of three real time DNA PCR tests in Q4 2022. As this report went to press, the database was in the process of being updated.

35 WHO (2022). "Strategic Preparedness, Readiness, and Response Plan: Monkeypox." Available at: https://cdn.who.int/media/docs/default-source/documents/health-topics/monkeypox/sprp-monkeypox-final-(05oct22).pdf?sfvrsn=711814b6_2&download=true. Accessed: November 29, 2022

to the FIND database, there are nearly a dozen commercially available rapid antigen diagnostics that indicate "regulatory achievement," per the database's categorization system. All of the rapid diagnostics that indicate regulatory achievement cite Conformité Européenne (CE). CE marking on a product indicates that the manufacturer or importer of that product affirms its compliance with the relevant EU legislation and the product may be sold anywhere in the European Economic Area. For diagnostics, the relevant legislation is the European in-vitro Diagnostics Directive 98/79/EC (IVDD)[36]. CE marking is not equivalent to SRA authorization, review or approval. Steps that could lead to such authorization were underway as this report was finalized in late 2022. In late November 2022, the US Food and Drug Administration (FDA) posted templates with what to include in Emergency Use Authorization (EUA) or pre-EUA submissions for mpox antigen diagnostic tests[37].FIND is initiating analytical and clinical evaluation studies for point of care mpox diagnostics including three antigen rapid diagnostic tests and two near-point of care molecular platforms, with three partner sites in the UK, Central African Republic and the Democrative Republic of Congo[38].

The primary diagnostic method of mpox virus globally is swab-based laboratory reaction (PCR) testing. Regulatory authorities have already examined data for and authorized the use of DNA polymerase chain reaction (PCR) kits in different countries. China's National Medical Products Administration (NMPA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) have authorized use of DNA PCR kits—two from the UK and one in China. The US Food and Drug Administration (FDA) has granted EUA for three real time DNA PCR tests as of December 2022.[39] There has been limited information on comparative performance of PCR kits during the current mpox outbreak; here, as with rapid antigen tests, the gaps are being filled in. A WHO-supported evaluation of eleven commercially available PCR kits for the detection of DNA from mpox (clades I, IIa and IIb), other orthopox viruses and variola virus[40].

The diagnostics landscape for mpox is, at presented, centered on lesion-based sampling. Swab-based laboratory polymerase chain reaction (PCR) testing is the primary diagnostic approach used today. The WHO recommended sample types are lesion exudate, roofs from more than one lesion, and lesion crusts. It is important to note that PCR tests have detected mpox infection in anorectal swabs obtained during routine sexually transmitted infection screening of asymptomatic (lesion-free) individuals. It is not yet clear if and/or how often asymptomatic individuals shedding virus may pass on the virus; as data on this question is collected, the use of diagnostics to inform vaccination strategies during outbreaks will need to be revisited and possibly refined.

At present, laboratory-confirmed mpox diagnostic capacity is centered largely in high income countries. Early in the outbreak, high-income countries such as the U.S. struggled with slow turnaround times of over 7 days before scaling testing. In low and middle- income countries, laboratory-based PCR capability is limited–a bottleneck that affects timely

36 "Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices," https://www.legislation.gov.uk/eudr/1998/79, accessed 13 December 2022.

37 US Food and Drug Administration (2022). "Monkeypox Emergency Use Authorizations for Medical Devices." https://www.fda.gov/medical-devices/emergency-use-authorizations-medical-devices/monkeypox-emergency-use-authorizations-medical-devices?utm_medium=email&utm_source=govdelivery#molecular. Accessed: December 13, 2022.

38 Personal Communication from FIND to UNITAID, December 8, 2022.

39 US Food and Drug Administration (2022). "Monkeypox Emergency Use Authorizations for Medical Devices." https://www.fda.gov/medical-devices/emergency-use-authorizations-medical-devices/monkeypox-emergency-use-authorizations-medical-devices?utm_medium=email&utm_source=govdelivery#molecular. Accessed: December 13, 2022.

40 Janine Michel, et al. "Evaluation of Eleven Commercially Available PCR Kits for the Detection of Monkeypox DNA." *MedRxiv.* October 19, 2022 https://www.medrxiv.org/content/10.1101/2022.10.14.22281096v1. Accessed 13 December 2022.

diagnosis and monitoring of a range of conditions.[41,42,43] While the WHO has distributed pre-designed PCR primer and probe test kits to LMICs without the laboratory capabilities to adapt published PCR primer and probe sequences, PCR testing infrastructure itself is limited in many LMICs. This limited infrastructure is often centralized in national laboratories or in additional urban areas, leading to slow test turnaround times, particularly in rural areas and, in all likelihood, under-counting of cases. There is therefore an urgent need to develop low-cost, accurate point of care diagnostics.

As part of the U.S. government's global mpox response, the U.S. Agency for International Development (USAID) reprogrammed USD$15 million and the U.S. Centers for Disease Control and Prevention (CDC) reallocated limited resources for diagnostic and laboratory capacity. These steps were taken after communication with health ministries of numerous low- and middle-income countries in South America, the Caribbean, and Africa to discuss their priorities and concerns regarding mpox control. The US officials coordinating this work reported relatively low demand for vaccinations and treatments from countries dealing with a range of other health issues and limited budgets for vaccination against a range of pathogens, some of which are deadlier than mpox. LMIC health ministries reported test result turnaround times of days and weeks, especially in rural areas. Such delays pose a serious challenge to a comprehensive epidemic control strategy. In low-income countries, including African countries where mpox virus is endemic and which experienced cases in the current outbreak, confirmatory diagnoses are rare– representing just a fraction of the total number of cases reported, with the majority recorded as "suspected.[44]" In Q3 2022, the Africa CDC began reporting confirmed cases only. Earlier reporting patterns suggest that this could result in under-reporting.

In addition, and while multiple primer and probe sets exist for in lab- real time PCR for detection of mpox virus, these primer and probe sets need to be validated in the current outbreak. Recent in silico and in vitro research found that a commonly used set of primers and probes, developed by the U.S. CDC and utilized by multiple commercial labs within the US, was found to have numerous sequence mismatches, which significantly decreased the limit of detection of the assay.[45] This recent finding further highlights the need for rapid, real world clinical validation of diagnostics in this epidemic. Furthermore, there is also a need to validate mpox diagnostics with samples of both clades of mpox. Because there are two clades of mpox, it is possible that some assays designed for just one clade may be less sensitive to the other clade.

As with COVID-19,[46] there is a need and demand both in high-income countries and low- and middle-income countries for inexpensive, rapid, point-of-care diagnostics for mpox. Access to these tests will, in many contexts, depend on the WHO creating and clarifying processes for emergency use listing (EUL) and pre-qualification (PQ) for in

41 Habiyambere V, Ford N, Low-Beer D, Nkengasong J, Sands A, Pérez González M, Fernandes P, Milgotina E. (2016, August 23). Availability and Use of HIV Monitoring and Early Infant Diagnosis Technologies in WHO Member States in 2011-2013: Analysis of Annual Surveys at the Facility Level. PLoS Med. 13(8):e1002088. DOI: https://doi.org/10.1371%2Fjournal.pmed.1002088. 1002088. PMID: 27551917; PMCID: PMC4995037.

42 Lecher SL, Fonjungo P, Ellenberger D, et al. (2021). HIV Viral Load Monitoring Among Patients Receiving Antiretroviral Therapy — Eight Sub-Saharan Africa Countries, 2013–2018. MMWR Morb Mortal Wkly Rep 2021;70:775–778. DOI: http://dx.doi.org/10.15585/mmwr.mm7021a2. Accessed November 29, 2022.

43 Ilesh V Jani, Trevor F Peter. (2022, August 15). Nucleic Acid Point-of-Care Testing to Improve Diagnostic Preparedness, *Clinical Infectious Diseases*, Volume 75, Issue 4, Pages 723–728. DOI: https://doi.org/10.1093/cid/ciac013. Accessed November 29, 2022.

44 See, for example, Africa CDC, "Outbreak Brief Number Fiv: Monkeypox in African Union Member States," August 11, 2022. https://africacdc.org/disease-outbreak/outbreak-brief-5-monkeypox-in-africa-union-member-states/. Accessed November 29, 2022.

45 Wu, Fuqing, et al. (2022, October 6). "Wide Mismatches in the Sequences of Primers and Probes for Monkeypox Virus Diagnostic Assays." *MedRxiv*, 2022. DOI: https://doi.org/10.1101/2022.08.10.22278644. Accessed 29 Nov. 2022.

46 Ilesh V Jani, Trevor F Peter. (2022, August 15) "Nucleic Acid Point-of-Care Testing to Improve Diagnostic Preparedness." *Clinical Infectious Diseases*, Volume 75, Issue 4, Pages 723–728. DOI: https://doi.org/10.1093/cid/ciac013. Accessed November 29, 2022.

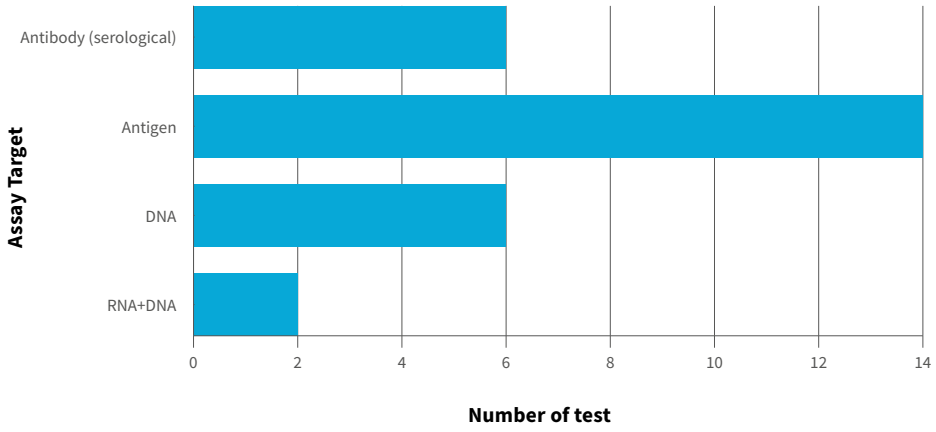
vitro diagnostics (IVDs) for mpox. As the WHO itself has pointed out, these processes are critical for access to IVDs in low- and middle-income settings and support manufacturers and donors in ensuring necessary technologies reach the populations that need them most.[47] For reference, please see WHO posted guidance for manufacturers for these processes for Zika,[48] Ebola,[49] and COVID-19.[50,51]

2.2 RAPID REVIEW OF EXISTING AND PIPELINE RAPID, POINT-OF-CARE DIAGNOSTIC TECHNOLOGIES FOR MPOX VIRUS

Methods

There are 22 such diagnostics listed in the FIND Database (See Figure 1). Isothermal molecular tests not classified as point of care (POC) or near point of care by the FIND Database have also been included in this landscape (see Table 2) on the basis of evidence that isothermal diagnostics can be used as POC or near-POC in many settings for various pathogens[52].

FIGURE II. Point of Care and Near Point of Care Assays in the FIND Database as of December 2022



(Numerical key: Six antibody tests, 14 antigen tests, six DNA and two RNA plus DNA)

47 WHO Prequalification. (2022) Benefits of WHO Prequalification of IVDs and MCDs. Available at: https://extranet.who.int/pqweb/vitro-diagnostics/benefits-who-vitro-diagnostics-prequalification. Accessed November 29, 2022.

48 WHO Prequalification. (2016, October 24) Instructions for Submission Requirements: In vitro diagnostics (IVDs) Detecting Zika Virus Nucleic Acid or Antigen. Available at: https://extranet.who.int/pqweb/sites/default/files/documents/161101_240_instructions_for_submission_requirements_ivds_detecting_zika.pdf. Accessed November 29, 2022.

49 WHO Prequalification. (2022) Ebola virus disease. Available at: https://extranet.who.int/pqweb/vitro-diagnostics/ebola-virus-disease. Accessed November 29, 2022.

50 WHO Prequalification. Invitation to manufacturers of in vitro diagnostics for SARS-CoV-2 to submit an application for emergency use listing by WHO. Last updated 11 March, 2022. Available at: https://extranet.who.int/pqweb/sites/default/files/documents/Invitation_Manufacturers_IVDs_COVID19_11March2022.pdf. Accessed November 29, 2022.

51 WHO Prequalification. (2022) Coronavirus disease (COVID-19) Pandemic — Emergency Use Listing Procedure (EUL) open for IVDs. Available at: https://extranet.who.int/pqweb/vitro-diagnostics/coronavirus-disease-covid-19-pandemic-%E2%80%94-emergency-use-listing-procedure-eul-open. Accessed November 29, 2022.

52 See, for example, Augustine, Robin et al. "Loop-Mediated Isothermal Amplification (LAMP): A Rapid, Sensitive, Specific, and Cost-Effective Point-of-Care Test for Coronaviruses in the Context of COVID-19 Pandemic." *Biology*vol. 9,8 182. 22 Jul. 2020, doi:10.3390/biology9080182; Khan, Pavana et al. "Isothermal SARS-CoV-2 Diagnostics: Tools for Enabling Distributed Pandemic Testing as a Means of Supporting Safe Reopenings." *ACS synthetic biology* vol. 9,11 (2020): 2861-2880. doi:10.1021/acssynbio.0c00359; Ocker, Ronja et al. "Malaria Diagnosis by Loop-Mediated Isothermal Amplification (LAMP) in Thailand." *Revista do Instituto de Medicina Tropical de Sao Paulo* vol. 58 (2016): 27. doi:10.1590/S1678-9946201658027. All papers accessed 13 December, 2022.

To supplement the FIND Database, this landscape conducted a rapid literature review to identify peer-reviewed and/or pre-print literature about point of care and near point of care mpox diagnostics to ascertain the extent to which the diagnostics on the market or in development had publicly available validation data. The review was done by searching PubMed, Google Scholar, the last 5 years of WHO smallpox working group meeting reports, commercial search engines, and commercial press releases for data related to orthopoxvirus diagnostics. The list of search terms used to identify papers included identifying information for all of the rapid antigen-based tests listed in the FIND database, to ensure that we did not miss relevant information on tests listed therein. The limited published data on assay performance identified by this literature review suggest that the rapid antigen tests that are presently on the market may not be sufficiently reliable to use as part of ongoing responses and in the context of new outbreaks.

The website links included in the FIND database for each assay were also visited, to ensure that no validation data had been missed. This two-way search approach confirms that validation data for the present array of mpox diagnostics, many of which are commercially available, is highly limited, and underscores the need for ongoing work by WHO and other partners to continue to validate tests. FIND emphasizes that the database relies on information from public sources provided to FIND by manufacturers and has not been independently verified and does not contain information about the quality of the tests.[53] The landscape did not look at antibody diagnostics, as they cannot be used to confirm active infection. Specific PCR primer and probe pairs also were not included.

In the narrative section that follows, Information on test chemistry, testing procedure, time to test result, validation and clinical performance (both the viruses and clinical samples used for validation, sensitivity, specificity, and limit of detection) were extracted and are presented here along with observations about what validation results suggest for the utility of its diagnostic class to aid in mpox virus detection and diagnosis. These observations are intended to prompt further discussion and action, and not as conclusive assessments. Importantly, the cost or feasibility of manufacturing reviewed diagnostics in LMICs was not assessed.

The literature review was supplemented with nearly a dozen interviews with researchers working on orthopoxvirus diagnostics, as well as officials at USAID and the U.S. CDC working on the global mpox response.

Results

The literature review identified seven peer-reviewed or pre-print publications describing mpox diagnostics that are actively in development. Three papers contained data on two rapid antigen-based diagnostics and five covered molecular, nucleic acid amplification diagnostics. (A paper on a molecular assay which is no longer in development was also identified[54]).

Table 2 summarizes the information on 32 tests: those found solely in the literature review (n=6[55]), those in the literature review and the FIND database (n=4), tests that are in the FIND

53 FIND. *Monkeypox Test Directory*. Last updated: 13 November, 2022. Available at: https://www.finddx.org/mpx-test-directory/. Accessed November 29, 2022.

54 For information on this assay, see Stern, D. *et al.* (2016) 'Rapid and sensitive point-of-care detection of Orthopoxviruses by ABICAP immunofiltration', *Virology Journal*, 13(1), p. 207. Available at: https://doi.org/10.1186/s12985-016-0665-5. The assay as described is highly complex but also highly sensitive; if simplified, this could be an additional approach to explore.

55 One paper (Institut Pasteur, Shanghai et al) describes three tests—a total of five papers on molecular diagnostics were identified.

database and have received Emergency Use Authorization from the FDA (3) and those tests solely in the FIND database (n=19).

Of the 14 rapid antigen-based tests listed in the FIND Database, 11 indicate "regulatory achievement" per the database's wording. As noted earlier, all of these tests indicate CE marking (Conformité Européenne) as the source of regulatory achievement. CE marking was until this year exclusively a form of self-certification by the manufacturer and is not equivalent to stringent regulatory authority approval. For example, in a review of 122 CE marked SARS-CoV-2 rapid antigen tests, researchers found that one in five CE marked tests had a sensitivity below 75%, with some CE marked tests failing to work at all. While new, more stringent requirements such as independent third-party validation were placed on CE marking in May 2022, the labels of the CE marked point-of-care or near-point-of-care tests for mpox in the FIND database do not indicate their CE marking has been obtained through the new IVD regulation[56]. Thus, manufacturer-provided information in the database affirms the need to explore additional regulatory review processes following validation.

TABLE III. Regulatory Status and Validation Data for Point of Care and Near Point of Care Mpox Diagnostics. Results from the FIND Database and Rapid Literature Review

Table Key: All diagnostics identified in the literature review (7) have footnote references and are described in detail in the results section.

Name	Type	Development Status	Validation Sample Type, Result if published	Possible Next Steps
Antigen Tests				
Vector Institute Orthopox Nanodot Assay[57]	Rapid Nanodot Assay	Research stage only	Cultured mpox virus & other orthopoxviruses, with various viruses as controls / vaccinia virus, ectromelia virus, and cowpox virus were detected in the range of 1,000-10,000 plaque-forming units per mL	Human sample validation
Tetracore Orthopox Biothreat Alert[58]	Lateral Flow Rapid Antigen Test	Commercially available for research use only	Human mpox & vaccina lesions from frozen samples / Sensitivity: 9/11 samples elicited a positive result; specificity: 10/11 non-orthopox samples elicited a negative result; limit of detection: 10 million plaque-forming units per mL	Additional human sample validation
Oxford Orthopox Antigen Test[59]	Lateral Flow Rapid Antigen Test	Research stage only	Modified vaccinia ankara (MVA) / limit of detection: between ~32,000 and 100,000 plaque-forming units of MVA	Human sample validation
Abiores Technology (Beijing) Co.,Ltd	Rapid Antigen Test	Commercially, available, CE-IVD mark	Lesion fluid; Serum; plasma; whole blood;/ No publicly available validation data	Validation and/or results' publication

56 "Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices," https://www.legislation.gov.uk/eudr/1998/79, accessed 13 December 2022.

57 Poltavchenko, AG et al. (2020) 'Rapid protocol of dot-immunoassay for orthopoxviruses detection.' *Journal of Virological Methods,* 113859. Available at: https://doi.org/10.1016/j.jviromet.2020.113859. Accessed November 29, 2022.

58 Townsend, M.B. *et al.* (2013) 'Evaluation of the Tetracore Orthopox BioThreat® antigen detection assay using laboratory grown orthopoxviruses and rash illness clinical specimens', *Journal of Virological Methods*, 187(1), pp. 37–42. Available at: https://doi.org/10.1016/j.jviromet.2012.08.023. Accessed November 29, 2022.

59 Ulaeto, D.O. *et al.* (2022) 'A prototype lateral flow assay for detection of orthopoxviruses', *The Lancet Infectious Diseases*, 22(9), pp. 1279–1280. Available at: https://doi.org/10.1016/S1473-3099(22)00440-6.

Name	Type	Development Status	Validation Sample Type, Result if published	Possible Next Steps
Autobio Diagnostics Co., Ltd	Rapid Antigen Test	Commercially, available, CE-IVD mark	Lesion fluid / No publicly available validation data	Validation and/or results' publication
Beijing Hotgen Biotech Co., Ltd	Rapid Antigen Test	Commercially, available, CE-IVD mark	Lesion crusts; Oropharyngeal swab; Saliva; Serum; Plasma; Whole Blood; / No publicly available validation data	Validation and/or results' publication
Bioantibody Biotechnology Co., Ltd	Rapid Antigen Test	Commercially, available, CE-IVD mark	Lesion roof; Lesion fluid; Serum / No publicly available validation data	Validation and/or results' publication
Dynamiker Biotechnology (Tianjin) Co., Ltd.	Rapid Antigen Test	Commercially, available, CE-IVD mark	Serum; Plasma; Whole Blood; Other / No publicly available validation data	Validation and/or results' publication
GenSure	Rapid Antigen Test	Commercially, available, CE-IVD mark	Lesion crusts; Oropharyngeal swab;	Validation and/or results' publication
Hangzhou Testsea Biotechnology Co.,ltd.	Rapid Antigen Test	Commercially, available, CE-IVD mark	Nasal swab / No publicly available validation data	Validation and/or results' publication
Joysbio (Tianjin) Biotechnology Co Ltd.	Rapid Antigen Test	CE-IVD, Research Use Only	Lesion fluid / No publicly available validation data	Validation and/or results' publication
NG Biotech	Lateral Flow Rapid Antigen Test	Research Use Only	Lesion fluid, other / No publicly available validation data	Validation and/or results' publication
Qingdao Hightop Biotech Co.Ltd.	Lateral Flow Rapid Antigen Test	CE-IVD	Lesion crusts; lesion roof; lesion fluid; Oropharyngeal swab;/ No publicly available validation data	Validation and/or results' publication
VivaChek Biotech (Hangzhou) Co., Ltd.	Lateral Flow Rapid Antigen Test	Late stage development - fully functional prototype	Oropharyngeal swab / No publicly available validation data	Validation and/or results' publication
Wuhan EasyDiagnosis Biomedicine Co., Ltd.	Lateral Flow Rapid Antigen Test	CE-IVD	Lesion fluid; Oropharyngeal swab; / No publicly available validation data	Validation and/or results' publication
Zhejiang Orient Gene Biotech Co., ltd.	Rapid Antigen Test	CE-IVD	Oropharyngeal swab; Other / No publicly available validation data	Validation and/or results' publication
Molecular Tests				
Abott Alinity m MPXV[60]	Real time DNA PCR for mpox Clade I/II	US Food and Drug Administration Emergency Use Authorization	Lesion swab speciments	
Roche Molecular Systems, Inc cobas MPXV for use on the cobas 6800/8800 Systems (cobas MPXV)[61]	Real time DNA PCR for mpox Clade I/II	US Food and Drug Administration Emergency Use Authorization	Lesion swabs	
Quest Diagnosics[62]	Real time DNA PCR for mpox Clade I/II	US Food and Drug Administration Emergency Use Authorization	Lesion swabs	
GeneXpert[63]	Cartridge based Molecular Test (real time PCR) non-variola orthopoxviruses	Awaiting regulatory submission & approval.	Lesion swabs and crusts from adults and children with mpox / sensitivity: 98.8%; specificity: 100%	Regulatory submission & approval

60 US Food and Drug Administration EUA letter to Abbott Diagnostics, October 7, 2022 https://www.fda.gov/media/162190/download , accessed December 13, 2022.

61 US Food and Drug Administration EUA letter to Roche Moledular Systems, November 15, 2022 https://www.fda.gov/media/163212/download, accessed December 13, 2022.

62 US Food and Drug Administration EUA letter to Quest Diagnostics, September 7, 2022. https://www.fda.gov/media/161454/download, accessed December 13, 2022.

63 Li, D. *et al.* (2017) 'Evaluation of the GeneXpert for Human Monkeypox Diagnosis', *The American Journal of Tropical Medicine and Hygiene*, 96(2), pp. 405–410. Available at: https://doi.org/10.4269/ajtmh.16-0567.

Name	Type	Development Status	Validation Sample Type, Result if published	Possible Next Steps
National Institute of Infectious Diseases of Japan and the University of Tokyo[64]	Isothermal Molecular Test	Research stage only, not commercially available.	Animal lesion and synthetic gene samples / Sensitivity: between 70-80% across different primer sets; Specificity: 100%	Human sample validation
University of Texas, Austin[65]	Isothermal Molecular Test	Research stage only, not commercially available.	Synthetic genetic fragments of virus from current outbreak / limit of detection: 8 copies of synthetic gene	Human sample validation
Twist Dx, Ltd.[66]	Isothermal molecular test (recombinase polymerase amplification assay for mpox virus)	Research stage only, not commercially available.	Serum and bloo samples from monkeys and humans/ Sensitivity (95% [43/45]) and specificity (100% [50/50]) were calculated by combining the validation results of both the monkey and human samples; standard DNA was used to calculate the limit of detection (16 DNA molecules/µl)	Additional human sample validation
Institut Pasteur, Shanghai and Collaborators[67]	Isothermal molecular tests (recombinase polymerase amplification assay with and without CRISPR and recombinase aid amplification with lateral flow test for mpox virus	Research stage only, not commercially available	Mpox DNA from lesion crusts obtained from people with mpox in pre-2022 outbreaks in Central African republic	Further evaluation and development.
BioFire Defense FilmArray Sentinel Panel	RNA+DNA (cartridge-based processing)	Research stage only, not commercially available.	N/A, no publicly available validation data	Validation and/or results' publication
BioFire Defense FilmArray BioThreat Panel	RNA+DNA (cartridge-based processing)	Research stage only, not commercially available.	Buccal swab, no publicly available validation data	Validation and/or results' publication
Guangzhou Wondfo Biotech u-card dx mpox virus test	DNA NAT reagent kit (proprietary platform)	CE-IVD mark	Unknown, no publicly available validation data	Validation and/or results' publication
SD BIOSENSOR STANDARD M10 MPX/OPX	DNA (cartridge based processing)	Early stage development (partial prototype)	Lesion crusts; lesion roof; lesion fluid; serum; plasma No publicly available validation data	Validation and/or results' publication
Ustar Biotechnologies EasyNAT Mpox Virus	DNA NAT reagent kit (proprietary platform)	CE-IVD mark	Purified DNA, no publicly available validation data	Human sample validation
Xiamen Biotime Biotechnology Co. Detection Kit for Mpox Virus	Real-time PCR	CE-IVD mark; MHRA UK approval	Lesion crusts; lesion roof; lesion fluid; wound swab; oropharyngeal swab; purified DNA No publicly available validation data	Validation and/or results' publication

64 Iizuka, I. *et al.* (2009) 'Loop-mediated isothermal amplification-based diagnostic assay for monkeypox virus infections', *Journal of Medical Virology*, 81(6), pp. 1102–1108. Available at: https://doi.org/10.1002/jmv.21494. Accessed November 29, 2022.

65 Bhadra, S. & Ellington, AD (2022) 'Portable nucleic acid tests for rapid detection of monkeypox virus', medRxiv, Preprint. Available at: https://doi.org/10.1101/2022.08.09.22278605. Accessed November 29, 2022.

66 Davi, S.D. et al. (2019) 'Recombinase polymerase amplification assay for rapid detection of Monkeypox virus', Diagnostic Microbiology and Infectious Disease, 95(1), pp. 41–45. Available at: https://doi.org/10.1016/j.diagmicrobio.2019.03.015. Accessed November 29, 2022.

67 Mao, Lingjing, Jiaxu Ying, et al. 2022. "Development and Characterization of Recombinase-Based Isothermal Amplification Assays (RPA/RAA) for the Rapid Detection of Monkeypox Virus" *Viruses* 14, no. 10: 2112. https://doi.org/10.3390/v14102112

Rapid antigen-based diagnostics

1. Orthopox rapid antigen test, UK Ministry of Defence and the University of Oxford[68]

Test chemistry

This test uses a cocktail of four monoclonal antibodies specific for African-Eurasian orthopoxviruses (variola virus, vaccinia virus, mpox virus, cowpox virus, camelpox virus, ectromelia virus, and taterapox virus). This test does not differentiate between the four orthopoxviruses.

As with all lateral flow tests, the specific antibodies are bound to a label (or a "tag") added to the nitrocellulose pad. The nitrocellulose pad also has a test line that consists of the same monoclonal antibody cocktail bound to the nitrocellulose paper. In addition, antibodies that bind to antibodies are also bound to the control line. Following addition of a sample containing orthopoxvirus antigen, the labeled monoclonal antibodies bind to the antigen in the sample. As they get wicked through the nitrocellulose paper through capillary action, the labeled monoclonal antibody antigen complex binds to the test line, causing a visible concentration of color on the test line, indicating a positive result. Regardless of whether there is antigen in the sample, the control line will always cause a concentration of antibodies, because it binds to a constant region on the labeled monoclonal antibodies.[69]

Test procedure

In this diagnostic, the virus sample is mixed with a buffer from a COVID-19 testing kit and applied to the nitrocellulose pad.[70] The procedure for this test is extremely simple and consistent with the widespread use of COVID-19 rapid diagnostics.

Time to test result

A result was recorded at 20 minutes after diluted virus was applied to the lateral flow assay.

Validation and clinical performance

Viruses and clinical samples used:

This diagnostic was validated using Modified Vaccinia Ankara virus, an isolate of the vaccinia virus, the virus used in first- and second-generation smallpox vaccines. Modified Vaccinia Ankara is replication incompetent in human cells and the Bavarian Nordic strain of this virus is used in the company's mpox vaccine.

At the time of publication, this diagnostic had not been validated using clinical samples. Professor Miles Carroll of Oxford University, the senior and corresponding author of the paper reviewed, recently attempted clinical validation of this diagnostic and was unsuccessful, with the diagnostic being unable to detect known positive mpox cases. However, further clinical validation and modifications to the assay chemistry are being attempted with a commercial diagnostic manufacturer.[71]

Sensitivity, specificity, and limit of detection (LOD):

68 Ulaeto, D.O. *et al.* (2022) 'A prototype lateral flow assay for detection of orthopoxviruses', *The Lancet Infectious Diseases*, 22(9), pp. 1279–1280. Available at: https://doi.org/10.1016/S1473-3099(22)00440-6.

69 E.g. *AIMS Microbiol.* 2020; 6(3): 280–304.

70 A COVID-19 test kit buffer was used because it was the easiest for these researchers to access; if commercialized, the buffer will likely not come from a COVID-19 testing kit

71 Krellenstein, J. (2022). Zoom conversation with Miles Carroll, 2 September, 2022.

Because this diagnostic had not been validated using clinical samples at the time of publication, clinical sensitivity and specificity could not be established.

The limit of detection was between ~32,000 and 100,000 plaque-forming units of Modified Vaccinia Ankara.

Next steps for diagnostic in development pipeline
Continued efforts to clinically validate and improve performance of this assay are underway. Given the *in vitro* promise of this assay, providing additional resources can further support its development.

2. Orthopox rapid antigen test, Tetracore, Inc.[72]

Test chemistry
This test uses monoclonal antibodies raised against vaccinia virus. No information is provided in the publication about the specificity and targets of these monoclonal antibodies. This test is a lateral flow test, the basic chemistry for which is described in the preceding test chemistry section.

Test procedure
In this diagnostic, the virus sample was mixed with a Tetracore, Inc. sample buffer and applied to the nitrocellulose pad. The procedure for this test is extremely simple and consistent with the widespread use of COVID-19 rapid diagnostics.

Time to test result
A result was recorded at 15 minutes after diluted virus was applied to the lateral flow assay.

Validation and clinical performance
Viruses and clinical samples used:

This diagnostic was validated by the U.S. CDC using between 100 and 100 million plaque-forming units per mL vaccinia virus, and between 100,000 and 100 million plaque-forming units of mpox virus. The test sample was 150uL aliquot.

Clinical samples were also used, including specimens from mpox, vaccinia, herpesvirus (Varicella and HSV-1) and parapoxvirus infections.

The results of the clinical validation should be interpreted cautiously, as the clinical samples, which were obtained from a CDC archive, are unlikely to be representative of what would be obtained in the field. Prior to being archived in the CDC library, these samples underwent an extensive process of grinding, sonication, freeze-thawing, and cleanup. Such specimen preparation is unlikely to occur in a point of care or near-point of care setting for use of this test and may significantly change the sensitivity and specificity of the test.

Sensitivity, specificity, and limit of detection (LOD)

Sensitivity: of the 11 vaccinia and mpox samples tested, 9 samples elicited a positive result. One false negative result was vaccinia virus; one false negative result was mpox virus.

72 Townsend, M.B. *et al.* (2013) 'Evaluation of the Tetracore Orthopox BioThreat® antigen detection assay using laboratory grown orthopoxviruses and rash illness clinical specimens', *Journal of Virological Methods*, 187(1), pp. 37–42. Available at: https://doi.org/10.1016/j.jviromet.2012.08.023. Accessed November 29, 2022.

Specificity: of the 11 non-orthopoxvirus samples, one sample (varicella virus) elicited a false positive.

10 million plaque forming units per mL was the reliable lower limit of detection, although some positive results were detected at 1 million plaque forming units per mL.

Next steps for diagnostic in development pipeline
This commercially available assay should be assessed in real-world conditions in the current outbreak and compared to gold standard q-PCR.

3. Orthopox dot-immunoassay from VECTOR[73]

Test chemistry and testing procedure
This test utilizes polyclonal sera derived from chinchilla rabbits immunized with vaccinia virus. The polyclonal serum is conjugated and attached to one spot on the nitrocellulose paper. A control is also provided. A complex series of washes are performed, and a colorimetric change indicates a positive result.

A separate set of polyclonal antibodies is conjugated with colloidal gold, as in a lateral flow test. A complex series of washes with solutions containing the gold conjugated antibodies are performed, and some washes without the antibodies. Then, a silver-containing developer solution is then utilized to increase the optical signal of the colloidal gold conjugated antibody dot.

Time to test result
The total time of the two-stage analysis is 60–70 min. A 39-minute simplified protocol is also possible with this assay.

Validation and clinical performance
Viruses and clinical samples used:

This test was validated with vaccinia virus, ectromelia virus, and cowpox virus. Controls used were chickenpox virus, measles virus, rubella virus. Controls did not elicit positive results.

Clinical samples were not used to validate this assay.

Sensitivity, specificity, and limit of detection (LOD)

Because this diagnostic had not been validated using clinical samples at the time of publication, clinical sensitivity and specificity could not be established.

Crude viral samples of vaccinia virus, ectromelia virus, and cowpox virus were detected in the range of 1,000-10,000 plaque-forming units per mL within 39 min. This is a superior limit of detection than the other three antigen tests reviewed.

Next steps for diagnostic in development pipeline
This assay's complex procedure could be optimized to make its procedure more user friendly. The developers of this assay are based at VECTOR, a Russian government agency. This may raise challenges for collaboration in the current context.

73 Poltavchenko, AG et al. (2020) 'Rapid protocol of dot-immunoassay for orthopoxviruses detection.' *Journal of Virological Methods*, 113859. Available at: https://doi.org/10.1016/j.jviromet.2020.113859. Accessed November 29, 2022.

Molecular, nucleic acid amplification diagnostics

1. GeneXpert non variola orthopox cartridge, validated by the U.S. CDC[74]

Test chemistry
The GeneXpert technology is standard q-PCR that uses primers that match a segment of a virus's genetic material. This technology is widely used and deployed in many health facilities in LMICs for HIV, TB, and malaria care, among other disease areas. This particular cartridge can distinguish between mpox and other non-variola orthopoxvirus in a single test. It utilizes the same primer probe set as the US CDC's 510k premarket cleared assay used in the US by CDC and commercial laboratories.

Test procedure
Two types of patient samples can be utilized for this assay: legion swabs and lesion crusts. Legion swabs are hydrated in phosphate-buffered saline (PBS); crusts are homogenized in PBS. Both are spun on a centrifuge and the resulting supernatant is eluted and 0.1 mL of fluid is loaded onto the GeneXpert cartridge.

Time to test result
The GeneXpert platform generally delivers results in 90 minutes or less.

Validation and clinical performance
Viruses and clinical samples used:

164 specimens from 161 suspected mpox patients were collected in the Democratic Republic of the Congo. 72 specimens were collected from adults; 89 were collected from children. Of these specimens, 114 were from pustular lesion swabs and 50 were crusts. 55% of specimens were positive for prevalence of MPX DNA via gold standard PCR; 37% specimens were negative; 8% were indeterminate.

Sensitivity, specificity, and limit of detection (LOD)

Compared to gold standard PCR, the GeneXpert mpox cartridge had a sensitivity of 98.8% and a specificity of 100%.

The limit of detection was not determined for this assay in this publication.

Next steps for diagnostic in development pipeline
Given the extensive and highly positive validation results of this assay, the next phase of development is submitting for regulatory approval (and to WHO if review enabled) to bring this assay to commercial availability.

2. LAMP mpox virus assay, the National Institute of Infectious Diseases of Japan and the University of Tokyo[75]

Test chemistry
LAMP is similar to PCR in that it works by amplifying specific segments of DNA of a pathogen

74 Li, D. *et al.* (2017) 'Evaluation of the GeneXpert for Human Monkeypox Diagnosis', *The American Journal of Tropical Medicine and Hygiene*, 96(2), pp. 405–410. Available at: https://doi.org/10.4269/ajtmh.16-0567. Accessed November 29, 2022.
75 Iizuka, I. *et al.* (2009) 'Loop-mediated isothermal amplification-based diagnostic assay for monkeypox virus infections', *Journal of Medical Virology*, 81(6), pp. 1102–1108. Available at: https://doi.org/10.1002/jmv.21494. Accessed November 29, 2022.

of interest. It is different from PCR in that no change in temperature is required. This means a simple heat plate is used for the reaction, rather than the complicated thermocycling device that changes temperature rapidly in PCR testing. LAMP is a highly specific, cheap, rapid and portable test.

LAMP reactions are generally insensitive to inhibitors or contamination than PCR, meaning that less purification of the sample is generally needed before running the assay.

Unlike PCR where a complicated method needs to be used to detect whether DNA has been amplified in the reaction, a LAMP reaction directly generates turbidity in the sample, allowing simple cameras to detect whether DNA has been amplified in the reaction. In addition to turbidity, changes in color can be used to indicate a positive result via pH sensitive dyes (presence of pathogen DNA will result in amplification of the DNA causing a resultant drop in pH).

Test procedure

In this assay, the DNA is purified from the blood and throat swab specimens using a commercially available DNA purification kit. The purified DNA is then added to the reaction. Presence of mpox DNA is determined by measuring the turbidity of the reaction solution.

Validation and clinical performance

Viruses and clinical samples used:

This assay was validated using peripheral blood and throat swab specimens collected from monkeys infected with Congo Basin mpox virus or West African mpox virus. It was not clinically validated with human samples.

Sensitivity, specificity, and limit of detection (LOD)
The sensitivity and specificity of three different primers were measured as follows:

COM-LAMP
Sensitivity: 80% (n=45/56)
Specificity: 100% (64/64)

C-LAMP
Sensitivity: 79% (19/24)
Specificity: 100% (24/24)

W-LAMP
Sensitivity: 72% (23/32)
Specificity: 100% (40/40)

The limit of detection was not measured using clinical samples. However, using plasmid DNA, the detection limits of the three different primers were measured to be as follows:

COM-LAMP: 100 copies/reaction of standard DNA
C-LAMP: 251 copies/reaction of standard DNA
W-LAMP: 1,000 copies/reaction of standard DNA

Next steps for diagnostic in development pipeline
This assay could be assessed in real-world conditions in the current outbreak and compared to q-PCR. LAMP assay sensitivity for other viruses, such as SARS-CoV-2, has been demonstrated to be near that of lab-based PCR.

3. LAMP assay by University of Texas, Austin[76]

Test chemistry and procedure
See explanation of LAMP assay chemistry and test procedure in the preceding section.

Time to test result
This paper reported that a result could be read after ~30 minutes.

Validation and clinical performance
Viruses and clinical samples used:

Synthetic gene fragments of the strain of mpox virus causing the 2022 outbreak were used to validate this assay. No viruses or clinical samples were used.

Sensitivity, specificity, and limit of detection (LOD)

Sensitivity and specificity could not be determined, as no clinical samples were used.

The limit of detection of the assay was exceptional, detecting down to 8 copies of synthetic gene fragments.

Next steps for diagnostic in development pipeline
Further validation is necessary to assess how well this assay will perform in a real-world clinical context. In particular, the level of nucleic acid purification and preparation that is necessary will be critical to assessing how well LAMP-based assays can be deployed in the point of care and near point of care context.

4. Recombinase polymerase amplification assay for mpox virus by Brandenburg Medical School Theodor Fontane and collaborators[77]

Test chemistry and procedure
Recombinase polymerase amplification is another form of isothermal DNA amplification, similar to LAMP (in that it is isothermal). Generally, reactions require simple heating at a constant temperature and can produce results in as little as 10 minutes. It is currently being developed by Twist Dx, Ltd. Detection of amplification can be determined using a fluorescent oligonucleotide probe or through the addition of an additional probe that can allow lateral flow strip detection.

To perform this test, blood or serum was added to a silica-based column DNA extraction kit to purify the DNA. Following the DNA extraction step, the DNA is added to the reaction mix, which was prepared from a freeze-dried, commercially available kit. The reaction is centrifuged, mixed, then centrifuged once more, and incubated for 15 minutes at 42

76 Bhadra, S. & Ellington, AD (2022) 'Portable nucleic acid tests for rapid detection of monkeypox virus', medRxiv, Preprint. Available at: https://doi.org/10.1101/2022.08.09.22278605. Accessed November 29, 2022.
77 Davi, S.D. et al. (2019) 'Recombinase polymerase amplification assay for rapid detection of Monkeypox virus', Diagnostic Microbiology and Infectious Disease, 95(1), pp. 41–45. Available at: https://doi.org/10.1016/j.diagmicrobio.2019.03.015. Accessed November 29, 2022.

degrees Celsius. Results were measured using a tube scanner device that measured the fluorescence of the probe.

Time to test result
In this paper, results from the reaction were recorded in 3-10 minutes. The total test procedure time was not reported.

Validation and clinical performance
Viruses and clinical samples used:

This test was validated using blood and serum samples from both monkeys (25 infected, 23 uninfected) and humans (20 positive samples, 27 negative samples). The human samples were taken from patients in Nigeria during the 2019 mpox virus outbreak.

Sensitivity, specificity, and limit of detection (LOD)

Sensitivity (95% [43/45]) specificity (100% [50/50]) were calculated by combining the validation results of both the monkey and human samples.

Standard DNA was used to calculate the limit of detection (16 DNA molecules/µl)

Next steps for diagnostic in development pipeline
Further validation is needed to determine the feasibility of this diagnostic to be used in point-of-care settings. Further validation using human clinical samples is also needed in preparation for regulatory submission and commercialization.

5. Three recombinase-based isothermal amplification assays (RPA/RAA) for the rapid detection of MPXV isolates by the Institut Pasteur, Shanghai and collaborators[78]

Test Chemistry and Procedures
The assays evaluated two recombinase-based isothermal amplification techniques: recombinase polymerase amplification (RPA) and recombinase aid amplification (RAA). It tested real-time RPA, RPA in combination with CRISPR-Cas12a (RPA-Cas12a) and RAA combined with lateral flow strips. See Diagnostics 2 and 4 for descriptions of RPA and RAA.

Time to Test Result
20-30 minutes

Validation and clinical performance
Viruses and clinical samples used:

Mpox virus isolated from lesion crusts of people who presented with mpox in previous outbreaks (prior to 2022) in Central African Republic.

Sensitivity, specificity, and limit of detection (LOD)
The limit of detection for the real-time RPA and RPA-Cas12a was 10^0 DNA copies per reaction for both assays For the RAA-LFS detection was successful for DNA copy numbers as low as

78 Mao L, Ying J, et al. 2022. "Characterization of Recombinase-Based Isothermal Amplification Assays (RPA/RAA) for the Rapid Detection of Monkeypox Virus." *Viruses*. 2022 Sep 23;14(10):2112. doi: 10.3390/v14102112. PMID: 36298667; PMCID: PMC9611073. Accessed 13 December 2022.

10^0 DNA copy/µL per reaction with clearly visible test and control lines. The specificity of the three assays was tested using 28 ng (about 10^9 copies) DNA of vaccinia virus, and 0.238 ng (about 3.8×10^5 copies) DNA of Varicella-zoster virus, and found to generate negative detection results.

Next steps for diagnostic in development pipeline

These results suggest that adaptation and combination of RPA/RAA and CRISPR-Cas technologies for the rapid, accurate, and convenient detection of mpox should continue, including with validation against human samples from the current outbreak to ensure sensitivity across clades.

2.3 DISCUSSION

Rapid antigen-based tests

Rapid antigen diagnostic tests (Ag RDTs), if they are sensitive and specific to accurately diagnose cases, could be a game changer in the diagnosis of mpox virus infection, especially in low- and middle-income countries. As the COVID-19 outbreak demonstrated in high-income countries, the convenience and ease of use for the Ag RDTs can allow testing to be far more accessible than a system which relies exclusively on tests performed in a centralized laboratory-based system. The comparison is not a perfect one, however. Unlike SARS CoV-2 rapid antigen diagnostics, which rely on saliva or nasal swabs, mpox Ag RDTs may require a swab or lesion sample which can be painful to obtain and, as of now, requires a health provider to do the sampling (several of the rapid antigen tests listed in the FIND database indicate oropharyngeal samples and/or nasal swabs used for validation, however the data are not available.

In the available literature, lateral flow tests had suboptimal performance characteristics, and relatively poor limits of detection (LOD) (varying by over an order of magnitude), with neither assay having an LOD below approximately 30,000 plaque forming units (PFU), roughly corresponding to a viral concentration of around 3 million virions. It should be noted, however, that the sample size on each validation was very small.

The immunofiltration assay and dot-immunoassay, which are also antigen tests but use different assay chemistry, demonstrated detected antigen at much lower concentrations of virus compared to the rapid antigen tests. However, these diagnostics are more complicated to use than a lateral flow test. The available performance data on lateral flow Ag RDTs suggests improvements will be needed to achieve reliability and sensitivity--for example with changes to the assay chemistry (*e.g.* sample buffer, capture antibody type, etc.). One team of investigators interviewed was working on this project with a commercial diagnostic manufacturer.[79]

Given that at least fourteen rapid antigen diagnostics are in development or commercially available globally, extensive “real world” head-to-head validation of these Ag RDTs can and should be performed promptly. Ideally, this would be done in coordination with WHO, public health agencies and research entities, tracking outbreaks in order to validate tests rapidly (as case rates decline, additional data will take longer to obtain and analyze.) Such head-to-head evaluation could compare the result of the RATs with a reference “gold standard” quantitative in-lab PCR-based diagnostic.

79 Krellenstein, J. (2022). Zoom conversation with Miles Carroll, 2 September, 2022.

Molecular diagnostics

In high-income settings, all laboratory-based diagnostics for mpox virus are nucleic acid-based diagnostics, primarily PCR. Nucleic acid amplification diagnostics have exceptional sensitivity and specificity, while at the same time having the shortest window period. However, in all settings, but especially poorly resourced settings, the staffing, reagent supply and mechanical requirements for current nucleic acid-based diagnostics such as PCR pose challenges to reliable access and rapid turnaround time.

Nucleic acid-based platforms like GeneXpert, LAMP, and recombinase polymerase amplification assays could be transformative, as they can achieve near or equal levels of sensitivity and specificity as in-lab PCR while being easier to use and easier to distribute at or near the point of clinical care. Of all point of care diagnostics reviewed, GeneXpert is both the most accurate and most mature in terms of validation. Furthermore, following validation and regulatory approval of the mpox GeneXpert cartridge, the preexisting distribution of GeneXpert machines in many LMIC settings to support HIV and TB diagnosis (among other diseases) may enable use of the GeneXpert orthopoxvirus assay to be scaled quickly. Engaging the company, and regulators, would be key to understand potential access to this product.

The existence of multiple sets of LAMP primers for mpox virus is also promising. The LAMP amplification process is *isothermal,* meaning that the process occurs at a constant temperature. The transformative potential for LAMP-based diagnostics was demonstrated by the COVID-19 pandemic. A LAMP-based diagnostic for SARS-CoV-2 testing, authorized by stringent regulatory authorities, is now commercially available. This diagnostic is cleared for use at home by non-medical personnel and has demonstrated comparable sensitivity and specificity to in-lab PCR for SARS-CoV-2.

2.4 CONCLUSION

This landscape identifies opportunities to rationalize and shape the mpox diagnostics field, including:

- **Continued WHO action to build global capacity for laboratory-based diagnosis that is integrated within surveillance and epidemiological systems.** WHO is presently working with technical partners to validate available assays, the majority of which, as this review confirms, have limited validation data available. WHO is also supporting scale-up of testing by shipping samples to referral laboratories, procuring commercial kits and primer/probe and positive control material for use in low and lower-middle income countries (LMICs) and sharing of testing materials.

- Following diagnostic validation, WHO emergency use listing for and/or pre-qualification of specific diagnostics could be considered in order to assist countries and other purchasers in identifying and making procurement decisions about commercially available tests. **The WHO's support of head-to-head evaluation of PCR kits provides valuable information; comparable information on rapid antigen tests, paired with assessment of cost and manufacturing parameters** that would impact scaling and commercialization will provide additional insights to inform decision making and and service delivery.

- **Exploration of diagnostic approaches to support routine, non-invasive screening, potentially as part of a multiplex assay.** At present mpox diagnosis requires a swab from a lesion and the test is conducted on the basis of symptoms and/or exposure reported by patients. Exploration of opportunities to incorporate mpox into standard point of care screening assays for sexually transmitted infection (STI) screening assays so that routine diagnosis for herpes simplex virus 2 (HSV-2), mpox and syphilis could be done with a single POC test. This is a priority that has been identified by the US government mpox coordinator as crucial to routinizing case detection in endemic contexts in the US; development of multiplex assays should not, however, be prioritized over the rapid development and evaluation of mpox tests, as the timelines for a multiplex assay may be longer..

- **Integration of PCR testing** for mpox using available platforms (Gene-Xpert), and guided by Diagnostic Network Optimization[80]. Even as rapid antigen diagnostic tests (Ag RDTs) and other tests are pursued, it will be important to develop rapid-integrated point of care PCR tests for mpox screening and monitoring especially amongst key populations (gay men and other men who have sex with men, transgender people, people with housing instability and living in congregate settings), and allow detection of infection and viral shedding in asymptomatic individuals.

The information gathered in this high-level analysis regarding diagnostics for mpox indicates that:

- In the context of the current mpox outbreak, **the pace at which rapid antigen tests entered the market outstripped global and national validation and regulatory approval**.

- **Diagnostics using LAMP in development for mpox could be an alternative to gold-standard PCR testing.**

- **Available diagnostics may not be adequate to ongoing outbreak detection**–especially if asymptomatic transmission emerges as a factor.

FINAL REMARKS

Even as mpox cases decline in many parts of the world that experienced new outbreaks in 2022, the need for a robust, reliable and affordable set of medical countermeasures remains. There is clear evidence that people living with HIV who are also immunosuppressed are at high risk of severe disease and hospitalization–mpox may become a new opportunistic infection, as well as a sexually transmitted infection. Given large populations of PLHIV in many LMICs who are out of care or not virologically suppressed, the need to ensure readiness for diagnosis and treatment is key, as is ensuring access to effective medical countermeasures in historically and newly endemic regions. This work must take place in the midst of competing priorities, limited budgets and divergent agendas with regard to pandemic prevention preparedness and response. This landscape offers ideas about priority areas and gaps with the hope that the mpox outbreak of 2022 is not consigned to a cycle of panic and neglect, but rather used as a catalyst for equity and action.

80 FIND, USAID, CDC, ASLM, IDC, BMGF. 2021. *Diagnostic Network Optimization: A Network Analytics Approach to Design Patient-Centred and Cost-Efficient Diagnostic Systems.* https://www.finddx.org/wp-content/uploads/2022/09/20220909_guide_to_DNO_FV_EN.pdf Accessed 13 December, 2022.